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### THE ROLE OF SURGERY IN THE TREATMENT OF CARCINOMA OF THE CERVIX\*

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I SHOULD, at the outset, like to express my appreciation of the honor you have done me in inviting me to take part in the evening's proceedings of this famous Society. I am deeply conscious of that honor, and my pleasure is the greater in that the subject under review is one which has interested me deeply. Coming as I do from the Chelsea Hospital for Women in London, I may claim to have served my apprenticeship in the Hospital in England which, led by those great surgical giants, the late Sir John Bland Sutton, the late Sir Comyns Berkeley, and Mr. Victor Bonney, can claim to have consistently led an all out surgical attack on the problem of gynecologic cancer in general, and of carcinoma of the cervix in particular. It is only in recent years that radiotherapy has modified this "all out" attack, and may I state initially that we still believe that some selected cases of carcinoma of the cervix are best treated by surgical methods.

In any discussion on the subject of the treatment of carcinoma of the cervix, division of opinion invariably centers around the relative merits of radiation and radical surgery. This generally applies only to cases coming within the category of Stages I and II. There is agreement that almost all Stage III and IV growths are unsuitable for treatment by radical surgery, though even in these it is possible to treat some by a combination of surgery and radiation. We have been interested in this respect in the recent publications of Dr. Meigs of Boston and of Dr. Taussig on the relative merits of the Wertheim operation and of pelvic lymphadenectomy, respectively, and it is upon these two aspects of the subject that I wish to speak in the main.

In many clinics the Wertheim operation was abandoned when radiotherapy in the form of radium application and deep therapy became generally established, but at my hospital the radical surgical operation has been practiced continuously, but in carefully selected cases only. The Sehauta hysterovaginect-

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tomy by the vaginal route has not been employed because of its neglect of the glandbearing area, and I personally have had no experience with the operation.

From a perusal of the records of the Chelsea Hospital for Women, it appears that the first radical abdominal hysterectomy for carcinoma of the cervix was performed by Bonney in 1907, and it must be remembered that at this time there was no adequate alternative method of treatment. The operation was performed with increasing frequency up to the late 1920's, by which time radiotherapy, with its low mortality and increasing efficiency, in part, supplanted surgery as a method of treatment. I feel, however, that in the present state of our knowledge there is still an important place for surgery in the treatment of carcinoma of the cervix, and my colleagues also believe this.

In his "all out" surgical attack on carcinoma of the cervix, Victor Bonney, between the years 1907 to 1936, performed 500 consecutive Wertheim operations. He has since passed the 600 mark. He operated upon all cases which were technically removable with the exception of a few in whom was present some condition which contraindicated operation. He began his series in 1907, when no other effective method of treatment was available and he continued throughout to operate on all operable cases. His operability rate so far as could be judged was 63 per cent of all cases seen, and his series included Stage I, II, and III growths. Unfortunately, analysis of the stage of advancement of the growth cannot be made, as this classification was not in existence over the greater part of his series. He found malignant involvement of the regional glands in 40 per cent of patients operated upon, and of the 500 patients subjected to surgery there were 70 operative deaths, a mortality of 14 per cent over-all.

In my submission, this work of Bonney's represents one of the most valuable clinical research investigations ever made in respect of carcinoma of the cervix. Not only does it show what surgery alone can do in such cases, but it has afforded us the first statistical evidence on a large scale of the incidence of malignant gland involvement. It has also shown that gland involvement is not absolutely dependent upon the stage of the growth in the cervix. While it is generally true that the more advanced the growth the more likely are the glands to be affected, this is by no means always the case, and advanced cases with little or no gland involvement have been frequently encountered, while conversely, some early cervical growths have shown extensive gland invasion.

Of the 500 operations, histologic examination revealed that in 300 patients the glands were free of growth, and in 200 the glands were involved. The five-year cure rate in the gland-free cases was 53 per cent, but when corrected, 58 per cent, and the corresponding cure rate in the gland positive cases was 22 per cent, or when corrected, 23 per cent. It is thus obvious that the prognosis is gravely affected by the presence of carcinomatous deposits in the regional glands. His over-all five-year cure rate is 41 per cent of the patients operated upon.

It must be appreciated that these figures for surgery apply only to the 63 per cent of cases which are deemed to be technically operable. There remains the further 37 per cent of patients who are beyond the hope of radical surgical extirpation of the growth, or in whom age and cardiac or renal insufficiency makes operative treatment inadvisable.

Bonney's figures of 14 per cent operative mortality are constantly quoted, but it must ever be remembered that this is a mortality rate resultant from an "all out" surgical attack on practically every technically removable growth. A further analysis of his figures shows that his operative mortality in the gland-free group is 10 per cent, whereas the gland involved group showed a figure of 20 per cent.

I quote these figures not because I consider the radical abdominal operation in general to be the best method of treatment of cervical cancer but because I wish to stress the results which surgery alone can accomplish in curing the disease.

A further analysis of Bonney's results, taking into consideration the 37 per cent of patients not subjected to surgery, shows an absolute cure rate of 25 per cent, or when corrected, 26 per cent. He estimates that if the proportion of cases favorable for radiation but unfavorable for surgery because of cardiac or renal disease or adiposity be added, his absolute total saving of life should be in the region of 30 to 31 per cent.

In none of Bonney's cases was radiotherapy employed routinely either before or after operation.

At this juncture it is interesting to compare the results which were being obtained by radiotherapy. The first reliable published results appeared between 1931 to 1933 (Table I). The five workers depicted publish a total of 2,583 patients treated up to 1926 with 614 five-year survivors, i.e. a survival rate of 23.8 per cent.

TABLE I. RADICAL ABDOMINAL HYSTERECTOMY (BONNEY). 500 CASES—1907 TO 1936

<i>Operability rate</i>	63 per cent of all cases seen		
<i>Operative mortality</i>	70	14 per cent	
Gland free group	300	Operative mortality	10 per cent
Gland involved group	200	Operative mortality	20 per cent
Percentage gland involvement	40 per cent		

TABLE II. RADICAL ABDOMINAL HYSTERECTOMY (BONNEY). 500 CASES—1907 TO 1936

<i>Cure rate—5 years—all cases</i>	40 per cent
Corrected cure rate.	43 per cent
<i>Cure rate, gland free cases</i>	53 per cent
Corrected cure rate	58 per cent
<i>Cure rate, gland involved cases</i>	22 per cent
Corrected cure rate	23 per cent
<i>Absolute 5-year cure rate</i>	25 per cent
but if cases favorable to radiation but unfavorable to surgery be added, he estimates the total saving of life to be 30 to 31 per cent	

TABLE III. RADIUM RESULTS PUBLISHED, 1931 TO 1933

YEAR	WORKER	PATIENTS	5-YEAR SURVIVALS	PER CENT
1931	Healey (U.S.A.)	1,574	352	22.3
1932	Regaud & Lacassagne (France)	317	107	33.7
1933	Gray Ward & Farran (U.S.A.)	343	85	24.7
1933	Kelly (U.S.A.)	349	70	20
	Total patients treated up to 1926	2,583		
	Total five year survivals	614	23.8 per cent	

TABLE IV. MARIE CURIE HOSPITAL (HURDON) 1942. RADIUM AND X-RAY THERAPY RESULTS.  
CANCER OF CERVIX

CLASSIFICATION	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
No. examined	40	174	455	167	836
No. treated	40	174	455	138	807
5-year survivals	32	107	143	10	292
Died of cancer	6	65	308	127	506
Died of intercurrent disease	2	2	4	1	9

TABLE V. MARIE CURIE HOSPITAL—LONDON (HURDON), 1942  
FIVE-YEAR SURVIVAL RATE—CARCINOMA OF CERVIX

	STAGE I	STAGE II	STAGE III	STAGE IV
Relative	80 per cent	61.5 per cent	31.4 per cent	7.2 per cent
Absolute	80 per cent	61.5 per cent	31.4 per cent	6 per cent

TEN-YEAR SURVIVAL RATE				
	STAGE I	STAGE II	STAGE III	STAGE IV
	63.6 per cent	41.9 per cent	22.4 per cent	2 per cent

The latest results published show an improvement in these figures when compared with the figures shown previously. More recently Richards of Toronto has published comparable results for radiotherapy.

From the foregoing, even the most biased surgical enthusiast must admit that over all and in general the results of radiotherapy are superior to those of surgery, in respect to operative mortality, possibly survival, but in spite of either method of treatment a considerable proportion of patients die from the disease. The problem now arises, can we salvage the lives of any of those patients who are destined to die even after adequate radiotherapy? In addition, is it ever desirable to employ surgical means without previous radiotherapy?

In a survey of the statistics relating to carcinoma of the cervix at the Chelsea Hospital for Women over the past twelve years, I find that the operation has been performed on 96 occasions, and that eight patients did not survive the operation, an operative mortality rate of 8.3 per cent. Further investigation reveals that this represents 14 per cent of all the patients presenting themselves with the disease. The highest operation rate in any one of these years was 20 per cent, and the lowest 9 per cent. Before the year 1936 on an average 55 per cent of the patients so presenting were treated by the Wertheim operation with an operative mortality of roughly 14 per cent. The year 1936 is taken as the dividing line, as it was in this year that the majority of the members of the Honorary Staff of the hospital decided to be more selective in their indications for the radical operation. It is interesting to note that just about 50 per cent of the mortality in the recent twelve-year period has been incurred by the few colleagues who have not been so selective in their indications for surgery. Had this careful selection been exercised, it is fair to assume that the operative mortality would have dropped to about 4 or 5 per cent.

This is in accordance with Dr. Meig's experience. Indeed, he published 91 consecutive operations without a postoperative death. My colleague Frank Cook and I, working independently at the Chelsea Hospital for Women and in our

other hospitals and nursing homes, have performed Wertheim's operation 207 times with six operative deaths, a mortality rate of under 3 per cent. This is not a tribute to any exceptional operative skill, but to a careful selection of cases, improved anesthesia, the use of blood transfusion and plasma infusions, the use of penicillin and the sulfonamides, and, not least of all, to good nursing.

Thus it will be seen that since 1936 on an average 14 per cent of the patients with carcinoma of the cervix have been subjected to the Wertheim operation, 9 per cent being the lowest in any one of the years, and 20 per cent being the highest rate. Previous to this 55 per cent of all cases presenting were operated upon, whereas Bonney in his own personal series considered that he operated upon 63 per cent of the patients presenting.

From the above it appears that operative treatment is now embarked upon in about one case in seven, whereas originally every alternate patient was subjected to surgery. Our selection of cases for the radical operation is confined to the cases shown in Table VI.

TABLE VI. INDICATIONS FOR WERTHEIM HYSTERECTOMY TODAY

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1. Radioresistant growths proved either clinically or cytologically (biopsy positive).
  2. Columnar celled carcinoma of the cervix.
  3. Stenosis of vaginal vault.
  4. The presence of large fibroids or ovarian cysts complicating cervical cancer.
  5. Salpingitis complicating cervical cancer.
  6. Refusal of radiation by the patient.
  7. Pregnancy complicating cervical cancer.
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*Radioresistance.*—So far as we know at the moment the most reliable method of determining radioresistance is on clinical grounds, and we have all met with the growth which fails to improve clinically after radiation or which, after appearing to heal, breaks down relatively quickly. Repeated biopsies confirm the diagnosis of resistance. Many attempts have been made on histologic grounds at an early stage of radiation to determine early resistance, and Koller working at the Royal Cancer Hospital and in association with the combined Cancer Clinic of the Chelsea Hospital for Women and the Royal Cancer Hospital bases his criteria of radioresistance on the effect of irradiation on mitosis as well as with its effect on surrounding connective tissue reaction. So far we have chosen to formulate the diagnosis of resistance on either clinical or biopsy evidence entirely.

*Columnar Celled Carcinoma of the Cervix.*—So far, in England, we have found these adenocarcinomatous growths very resistant. At the Chelsea Hospital for Women only 10 per cent survived over five years after radiation. Maliphant of Cardiff finds 14 per cent five-year survivals, and Professor Windeyer from the Middlesex Hospital reports about 14 per cent survivals. In a small personal series of eleven such cases which I have followed up after the Wertheim operation, so far four, or 36 per cent, are alive and well after a period of five years. In this respect also we have noted that the squamous endocervical growth appears more resistant than the more common exocervical growth.

*The presence of large fibroids, ovarian tumors, or salpingitis* in our opinion always contraindicates radiation, and all such cases are treated surgically if the patient's condition permits.

*Vaginal vault stenosis due to congenital or acquired lesions* makes adequate radium application impossible, and *refusal of radiation* by the patient is occasionally encountered.

*Pregnancy complicating cervical neoplasm* is a serious matter, and opinions vary as to the best method of treatment. Technically the operation during pregnancy is more difficult as the vascularity of the parts makes oozing more troublesome, though this is to some extent offset by the pliability of the tissues. I have performed Wertheim's operation on three occasions during pregnancy, and one of these patients has survived eight years. The other two patients died within one year of widespread recurrence.

*Wertheim's Operation After Previous Irradiation.*—On sixty-two occasions I have performed the operation after previous radiation by radium alone, or by a combination of radium and deep x-ray therapy. The intervals between radiation and operation have ranged from one week to fourteen months. This latter was an unusual case which had been fully radiated by local radium and two full courses of deep therapy under the care of Professor Windeyer of the Middlesex Hospital. The patient persistently gave a positive cervical biopsy for adenocarcinoma, and in the end he asked me to attempt a radical abdominal hysterectomy. This was accomplished without any real difficulty together with a thorough clearance of the glandbearing area. The cervix showed undoubtedly active adenocarcinomatous changes, but the glands were negative for growth, and I am quite sure that they had never been involved. In the main, previous radiation does somewhat magnify the technical difficulties of the operation, but, provided the growth still conforms to Stages I or II, in my experience it is always removable. In my opinion it is more than justifiable to attempt such cases, as the alternative to operation is death.

*Results of Wertheim Hysterectomy on Cases Selected as Unsuitable for Radiation or Found to be Radioresistant.*—During the years 1936 to 1941 in the Chelsea Hospital for Women fifty-four operations were performed in such cases. In all there were 34 Stage I and 20 Stage II growths, and at the end of five years 24 patients, or 44.4 per cent, of the total were known to be alive and well. Six were lost in the follow-up during the first three years of the war. If these be excluded it will be found that 50 per cent of the patients followed up were alive and well. There were three operative deaths in the series—a mortality rate of 5.5 per cent. It must be remembered that these cases were selected as being either unsuitable for radiation or as being proved radioresistant cases. The number who would have survived without operation is impossible to assess.

*The Regional Glands.*—So far as we can assess, we have come to the conclusion that the rate of carcinomatous gland involvement is approximately as follows:

Stage I	20-25 per cent
Stage II	30-35 per cent
Stage III	40-50 per cent
Stage IV	Over 60 per cent

These figures are based on material obtained from the Wertheim operation, from the operation of lymphadenectomy without removal of the uterus and from autopsy material, and these figures appear to agree with some other observers.

It would appear obvious that treatment by radium alone using vaginal applicators only can never hope to give adequate radiation to the lymphatic field of the pelvis. Some workers even question the efficiency of deep ray therapy in this respect. At the risk of incurring the enmity of the radiotherapists here I make so bold as to suggest that this ability to sterilize the pelvic lymphatic field of carcinomatous deposits is not so great as many of them think. I feel so strongly about this that I often wonder if the improvement in the results of

radiotherapy are not due more to improvements in the details of application, screenage and dosage of the radium rather than to the addition of deep x-ray therapy. Indeed, the latest five-year report of the Holt Radium Institute in Manchester shows better results in Stage I and II growths with radium alone than with combined radium and deep x-rays.

However, their numbers are relatively small. One must confess that these results are at variance with those usually shown for other centers, but Dr. Paterson of Manchester is unusually meticulous with his radium applications, and he certainly obtains the maximum intensity of radiation to the cervix and its neighboring structures from his vaginal radium application.

TABLE VII. RESULTS OF WERTHEIM'S OPERATION AT THE CHELSEA HOSPITAL FOR WOMEN FOR THE YEARS 1936 TO 1941, INCLUSIVE

	STAGE I	STAGE II	STAGES I AND II
Number of cases treated	34	20	54
Number alive at end of five years	14-41 per cent	10-50 per cent	24-44 per cent
Lost in follow up	5	1	6
Number alive after five years excluding lost cases	14-48 per cent	10-53 per cent	24-50 per cent
Operative deaths			3
Operative mortality			5.5 per cent

TABLE VIII. HOLT RADIUM INSTITUTE (MANCHESTER) 1945. CANCER OF CERVIX. 771 CASES. 1932 TO 1939  
RADIIUM TREATMENT WITH AND WITHOUT X-RAY THERAPY

TECHNIQUE	STAGE I		STAGE II		STAGE III		STAGE IV	
	NO.	5-YEAR SURVIVALS	NO.	5-YEAR SURVIVALS	NO.	5-YEAR SURVIVALS	NO.	5-YEAR SURVIVALS
A. Radium and x-rays	23	62 per cent	224	44 per cent	212	29 per cent	55	20 per cent
B. Radium alone	35	76 per cent	117	49 per cent	58	25 per cent	27	8 per cent

In this respect also I have had some experience of performing lymphadenectomy after a full course of treatment by radium and deep x-rays. I have found a cured cervix with negative biopsy in association with positive lymph nodes apparently unaffected by the deep therapy. In all those cases (37) in which the lymph nodes have proved negative for carcinoma, they have been so mobile and so easily removed that I cannot believe that they have ever been involved. I have never yet removed adherent lymph nodes which have been obviously sterilized by radiation and which have been proved to be free of growth.

Likewise I have yet to see a recurrence following the Wertheim operation successfully treated by deep therapy, and this has also been Mr. Bonney's experience.

We must accept the fact that in up to 80 per cent of Stage I growths the glands are unaffected, in up to 70 per cent of Stage II growths they are free, and in more than 50 per cent of Stage III growths there is no malignant involvement. Is it in these gland-free cases that the radiotherapist obtains his successes? No one will doubt that the adequate application of radium will cure the majority of the local cervical growths, but to my mind it is not yet proved how efficient is deep therapy in eradicating the disease from the glandbearing area. I feel with Dr. Taussig that there is a place for lymphadenectomy in selected Stage III cases which have been cured locally by radium, and I feel that such a procedure could well be extended to include Stage II cases and selected cases of Stage I growth. In such cases the operative mortality is negligible, and my

colleagues and I have decided to extend the practice of lymphadenectomy until such time as improvements in deep therapy or some other more effective method of treatment makes the procedure unjustifiable and unnecessary.

*Technique of the Wertheim Operation.*—It perhaps will interest you to outline a few of the technical modifications of the Wertheim Operation practiced in our hospital. Anesthesia is obtained by the use of intravenous pentothal followed by gas and oxygen combined with spinal analgesia using light perecaine intrathecal solution. Recently we have tried the use of gas, oxygen, and curare, but so far this has not proved popular. Most of us perform the lymphadenectomy early in the operation, immediately after making certain that the bladder can be satisfactorily displaced downwards. One of my colleagues, Aubrey Goodwin, practices lymphadenectomy early in the operation sweeping the glands medialwards and leaving the iliac and obturator lymph node chain attached to the uterus throughout. This early attack on the lymph glands facilitates early exposure of the ureters and uterine vessels, allows of better hemostasis, and has the psychological advantage in that it gives the surgeon a sense of completion as soon as the uterus with its attachments has been removed. I also have the impression that operative shock is somewhat lessened.

At least the upper one-half, and preferably the upper two-thirds of the vagina, are removed, and if this clearance be effected vaginal recurrence is almost unknown. The vaginal vault is left open for drainage purposes and the subperitoneal raw area is lightly packed with penicillin gauze, one end of which passes through the vagina. This gauze is removed in thirty-six hours. Plasma infusion or blood transfusion is practiced in every case as a routine, and the choice of solution depends upon the amount of blood lost.

The ureters and bladder are treated with the greatest gentleness and respect, and this is especially important in the post radiation cases. Over the past twelve years the incidence of postoperative urinary fistulas has been 3.1 per cent, a figure which compares favorably with that of fistulas following radiotherapy.

### Conclusions

I trust that I have not given the impression that I do not appreciate the value of radiotherapy, but I do feel that there has lately been a tendency to take a broader view of the whole subject and to treat each case on its merits. In recent years radical surgery for the condition has tended to be underrated in its usefulness. The operative mortality in properly selected cases should not exceed 5 per cent, and should never reach the high figures sometimes quoted. The figures given for radiation always tend to favor that form of therapy, as the five-year results are always described as "survivals" and not as "cures." Indeed a large percentage of five-year radiation survivals are literally dying of cancer of attenuated virulence. The ten-year survival rate shows a very appreciable drop, and even after this time a considerable percentage of patients die of the remote sequelae of radiation. In following up these postradiation cases, the interpretation of thickening and infiltration is difficult to assess. The radium enthusiast calls this "fibrosis," the surgical enthusiast designates it as "recurrence" and the honest observer simply states that he does not know. After the Wertheim operation any thickening denotes recurrence, and the falling off in the figures of ten-year results is not nearly so great as in the case of radiation. Bonney estimates that between five and ten years he loses a further 10 per cent from recurrence.

Let me again stress that in my view in the present state of our knowledge the routine treatment of election for the average case of cancer of the cervix is by radiotherapeutic means, but that in certain selected cases there is a place for surgery which in these cases offers the best prospect for the patient. In addition I suggest that the more extensive practice of lymphadenectomy, especially in Stage III cases, might improve our results. It would at least enable us to assess the real value of deep therapy on the pelvic lymphatic glands if it were practiced as a routine after a course of such therapy. The pressing need at this moment is an investigation of 1000 consecutive lymphadenectomies after x-radiation.

I submit that the absolute cure rate in carcinoma of the cervix can be increased by a surgical approach to those cases which prove to be radioresistant or in which adequate radiation is not possible.

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### Discussion

DR. WILLIAM P. HEALY.—“When talking about carcinoma of the cervix, Dr. Read speaks the same language that we do, and there is certainly no room, in my opinion, for destructive criticism of anything that the doctor has said, and constructive criticism is merely endorsement of the paper.

“I was very much interested in the slide in which Dr. Read referred to the indications for the Wertheim operation of hysterectomy. I think I might endorse all of it except possibly the final one about pregnancy as a complication of carcinoma, or carcinoma as a complication of pregnancy, but then Dr. Read has only had three cases which, of course, is not a very large percentage, so I won’t discuss that because my colleague, Dr. Smith, has gone into that subject and is more competent to discuss it than I. However, with Item I I agree completely; it endorses all that we were teaching when I was at the Memorial Hospital as a reason for surgical interference in carcinoma of the cervix. We gave deep roentgen therapy first, and when the lesion in the cervix failed to show a response in ten or twelve days we knew we were dealing with a radioresistant lesion, clinically speaking, and, histologically, it could, of course, be demonstrated as readily. When the lesion, after apparently responding, breaks down and ulcerates again, you have a lesion which is not going to do well under radiation therapy.

“Then there is the third group. You may not cure those cases by operation, but you will at least cure the patient of the local recurrence with the persistent foul-smelling vaginal discharge and subsequent hemorrhage by doing a hysterectomy, and in a small percentage the patients will probably be cured.

Dr. Read very kindly showed in one slide the series of cases that I reported in 1930 or 1931, a total of 1,574 carcinomas of the cervix. That brings to my mind his second group of adenocarcinoma or columnar cell cancer of the cervix, in which he feels that there is a definite indication for hysterectomy. If my memory is correct, I reported 42 adenocarcinomas of the 1,574 cases, and the end-results in our series were not at all influenced by the histologic or the clinical setting of the case, and the advanced cases gave an equivalent percentage, clinically speaking. In other words, putting it this way, Stages I and II League of Nations and III and IV adenocarcinoma behaved exactly as the squamous cell.”

At this point Dr. Healy stated that they feel in cases of carcinoma of the cervix the important point, especially in advanced cases, is whether they are favorable for operative treatment or not, and that in their experience the end-result was in accordance with that. Continuing, Dr. Healy said:

"Dr. Read also mentioned that he finds they operate in about 14 per cent of their cases. That is remarkably interesting, and if I am not right about that he will correct me, because our figures show that those are the justifiable cases in which to operate. I think about 15 per cent of our cases at the Memorial Hospital as we examined them and classified them in the League of Nations group were regarded as very favorable cases in which you might consider surgical intervention and, of course, we were depending on radiation except where we met with radioresistant cases, and in those we always recommended surgery.

"I want to express my deep thanks to Dr. Read for his splendid presentation, with all of which I am in hearty agreement."

DR. HOWARD C. TAYLOR, JR.—"Like Dr. Healy I am impressed by Dr. Read's paper because he speaks from experience of a service reporting 600 or 700 cases, thus he has the advantage of an opinion which is predicated on the basis of a large experience. What strikes me, however, is that Dr. Read is making the opposite point here in New York from that which I think he perhaps intended to make. I gather that this paper was written, at least in part, to defend the position of surgery in the treatment of cancer of the cervix, and in his institution he has shown a great reduction from an operability of 63 per cent to 14 per cent. Consequently he comes to us, not as an apostle of surgery, but warning us against our present trend towards the extension of surgery. I may be wrong about that and may be putting words in his mouth, but I came here and received a totally different impression from what I expected as he pushed me in an entirely opposite direction from that which I anticipated.

"The question of what group to operate on and what group to assign to radiation is one which has received a great many different answers, and it is only with some difficulty that we can squeeze them into three or four different categories representing certain different schools of thought in relation to the indications for this disease. The first one is put into the surgical group, those which are extremely favorable from the standpoint of the extension of the disease. It is my impression that Meigs has done that because his operability runs about 10 per cent and includes, in general, the earliest cases. This grouping to me, seems illogical because he is changing the operability in that group of cases in which the results of radiation are the very best."

Citing the slide shown by Dr. Read from the Marie Curie Hospital, where radiation in Stage I carcinoma was as high as 80 per cent, Dr. Taylor stated that this means, if we are to consider the cure rate from radiation therapy to be 80 per cent in this category, that surgery would have to do better than 80 per cent. However, he said that, in his opinion, he did not think the cure rate in cancer will be much improved by changing the method of treatment, in 10 per cent of these particular cases, to radiation therapy. Continuing his discussion, Dr. Taylor said:

"Dr. Read has indicated a different method of selecting cases for operation, and those are the ones with very special indications, such as cases which appear to be radioresistant, and he wasn't quite sure whether he was able to judge radioresistance on the basis of type or the basis of preliminary x-ray treatment and trial of radiation therapy. In so far as that group is concerned, I would be very much interested in discussing it with the pathologist.

"In the second group of radioresistant cases the doctor presents special indications, such as the complication of pregnancy, stenosis of the vaginal vault, and one or two others. I think that type of selection is based on a very considerable degree of experience for the reason that that is a high degree of selectivity based on intuition and personal experience and with great difficulty reduced to statistical analysis. I would suggest that he will have difficulty in handling the material statistically in the future because, on the basis of selectivity, it will be extremely difficult to duplicate in other institutions.

"In so far as salvaging cases in the third group is concerned, this is where we compare the value of surgery in respect to the second and third group and (in the latter group) the operability in this country is about 45 per cent." In group 3 Dr. Taylor observed that Dr. Read was predicating his opinion on the basis of his experience, which admittedly was not large, and added that, logically, he, personally, "always thought that operability should include those cases in which lymph nodes are involved, but capable of removal. That is the group in which, theoretically, surgery may cure a certain percentage of patients, whereas x-ray therapy will probably not cure any. It is doubtful whether radium in the cervix will reach the lymph nodes. Therefore, I think, on the basis of operability, we should not include the 10 per cent where only a very few lymph nodes are involved and there is a high percentage of radiation cures." Dr. Taylor now commented on the second and third group, which constitute a large number of cases, including those of the operable variety, without lymph node involvement, and stated that here is where you would expect a difference in the results between radiation and surgery, and that operability would vary between 40 and 50 per cent.

Continuing his discussion, Dr. Taylor said:

"The other point is, of course, increased operability with the Wertheim operation. We have not had enough experience with this procedure to speak with certainty, but I submit these different categories which may be considered in separating and evaluating the results between radiation and surgery.

"In closing, I am impressed that Dr. Read has reduced his operability to about 14 per cent. From the pathologic standpoint, however, I feel it should be around 40 per cent."

DR. GEORGE GRAY WARD.—"I am heartily in agreement with Dr. Read's general statements.

"The difficulty, of course, is that which we experience in determining Stage I, II, and III cases. For example, it is very hard always to know whether the infiltration that you may feel is inflammatory or carcinomatous. In some cases it is not possible to palpate the deep glands in the upper higher pelvis. Therefore, while apparently a case may be Stage I as you see it from below, it really may be further advanced from what you thought at firsthand.

"A group of us went abroad in 1912 and learned the technique of the operation from Wertheim, Franz, and Bumm, and other men who were doing this work in Germany, and on our return we practiced the operation here. In 1919 we abandoned it for radium. We have given six reports of our five-year salvage at the Woman's Hospital. Our first rate was something like 23 per cent total salvage. We have completed a seventh report, which has not as yet been published, and in this report in 217 cases our salvage rate is 35 per cent. This includes all cases, both early and late, and for the early cases, 61.5 per cent, which was quite a marked improvement over our first report. The primary mortality was 1.28 per cent. We had 15 cases in the series which were stump carcinoma cases, and we had some 46 per cent of cures.

"In the treatment of stump carcinoma Scheffey and Behney, of Philadelphia, as well as we, feel that the results in these cases are better than where the whole uterus is in place. Very often hysterectomy is done, leaving the cervix behind, and ultimately the patients develop cancer and these patients generally respond quite favorably to radiation.

"After all, the early cases are the ones requiring the Wertheim operation, but the average general surgeon or the average gynecologist is not trained in the technique of that operation, therefore radium undoubtedly will be relied upon in a great proportion of these cases, but there is no question that in the early cases, as Dr. Read says, the radical Wertheim operation or the extraperitoneal resection of the glands, or the Taussig operation, combined with radiation, will give better results."

DR. JAMES A. CORSCADEN.—"The adjective that comes to my mind is 'impressive.' This is a story of forty solid years in the study of this disease. I don't know of a similar study that has been carried on by any other group.

"There is only one technical point of interest to me and that is the matter of the lymph nodes. As I remember Wertheim's work, he dissected the glands and did a large number of serial sections of the glands and found when the regional lymph nodes were involved,

the distal nodes were also involved. That is my recollection. Clark improved in Wertheim's technique, but definitely thought it was not necessary to remove the glands if distal glands were involved. I would like to be corrected in that if I am wrong.

"In so far as radiation of the lymph nodes is concerned, Dr. Gusberg and I last year became interested in the technique of using interstitial radiation. One of the first things we tried to do was to ascertain how much radiation arrived at the lymph nodes by various technique as we know them from many studies; that of Nolan, for example, and my recollection is that it amounted to about one-half. So the question of radiation or sensitiveness to radiation of the lymph nodes is one in which I feel we should think of in terms of the lethal dose.

"Those are the only two points I have in mind (there is a possibility that I may be wrong): one, Wertheim's experience with lymph nodes, and, secondly, the fallacy of saying that the lymph nodes are not affected by radiation because as we studied them, they are affected."

DR. FRANK R. SMITH.—"No one could hear this delightful presentation without being impressed by Dr. Read's sincerity in the presentation of his facts, and I would like to thank him for it; I enjoyed every minute of it.

"You cannot help but be impressed by the futility of using percentage figures, especially where there is any selected material for the reason that there is human equation involved, and that differs where we use a clinical estimation of the stage of the disease, and that is one thing surgery has done in this disease; it has shown us how wrong we have been many times in our clinical estimation of the stage of the disease.

"I was interested in one of the slides the doctor showed in which it looked as if in surgery the more advanced the disease the better the results from lymphatic dissection.

"Dr. Smith then said that Stage I showed 41 per cent (of cures) and then changed it, as best could be understood, to 53 per cent for Stage I, or that figure for Stage II, and as far as Stage III was concerned, he said he forgot what that showed.

"I was also interested in Dr. Taylor's estimation of operability which is a good physiologic thought. Various people talk about operability, but it differs with different clinics. In this respect I was struck by Bonney's operability of 63 per cent as compared with Dr. Read's of 14 per cent. That is very interesting. It would also be of interest to know how many of his patients were radiated previous to operation, and whether they should be classified as primary operability or not. At Memorial Hospital we have no primary operability; all patients are radiated before operation.

"Before showing two slides, I would like to quote Dr. Kosmak and state that these are the opinions of the author and the Journal takes no responsibility for them.

"I simply present these slides to show the incidence of the various types of carcinoma, taking in Dr. Healy's regime in the first section, from 1922 to 1924. A, or Stage I, shows an increase, due perhaps to increasing publicity and better education of doctors; and B, or Stage II, shows an increase; Stage III diminishes, as would be expected, while Stage IV is about the same. In spite of improvement in material, we find pretty much of a plateau; that is, in recent years there has been a plateau in the results obtained by radiation. That was the reason we utilized the surgical approach to this disease at Memorial Hospital, to see if we could improve the cure rate. Now, if we take the two types Dr. Taylor so ably presented, the favorable operability, Stage I and II, and operated on them, giving them radiation at the same time and postoperative radiation, preliminary radiation being given at the present time by the vaginal cone, unless we appreciably improve our over-all statistics in those two groups, the question arises as to whether we are justified in putting the patient through a major surgical procedure as a substitute for the simple insertion of the radium pack. In other words, if our mortality is greatly increased, are we justified (in subjecting the patient to operation)?

"The second group is that in which there is a feeling of discouragement, in which we take the position that all we can do is palliate. In Stage III the salvage rate is low. In Stage IV we never have been able to do very much.

"There is some justification in the so-called 'noble experiment' at Memorial Hospital. Today we attempt surgery for these people, but we must definitely ask ourselves the following questions: One, do we salvage appreciably any group of people who were not salvaged before? Secondly, do we make the patient more uncomfortable than we do with palliative radiation? Third, is the mortality much greater? Fourth, what is the time of palliation?

"I note that in Dr. Read's Stage III group, 22 patients, none lived eighteen months. Dr. Healy will tell you that we have had many of these advanced cases, so-called, clinically speaking, who have lived eighteen months or longer.

"If we are going to evaluate this so-called noble experiment, we must ask ourselves these questions.

"Since September 15 all patients with cancer of the cervix, whether they have Stage I, II, III, or IV, who have entered the wards of the Memorial Hospital have been treated surgically. There have been only three cases in which exploratory operation has been done. They had strange complications; one had deep metastasis in the liver, which is unusual, the second had complete involvement of the iliac vessels which infiltrated these particular structures, and the third had peripancreatic disease all around the upper abdomen." At this point, Dr. Smith referred to what sounded like "peritoneoscopy," which he said another man called "devisceration, which I think is just as bad," and spoke of transplantation of the ureters along with other points of the technical procedure, the ureteral transplantation being done at the "same stage," and added that radium is left in the colostomy loop in these cases in which the rectum has been removed. "The over-all mortality," Dr. Smith remarked, "is 25 per cent of all patients." This mortality, however, the doctor said, could, if desired, be corrected, but the reporter was unable to get the corrected figure. "One patient died suddenly on the ninth day, I think, but no one knows what she died of. Up to that time she had been doing well. Even autopsy failed to disclose the cause of death."

At this juncture, reverting to a previous observation, Dr. Smith said, "Although it presents obvious danger, I still think it is a noble experiment. I am not speaking critically in respect to it, but it is surgical calisthenics unless it fulfills the qualifications I have stated. I do not believe we can talk about it until enough time has elapsed to show if it fulfills the qualifications. There is a bad effect about it. I think that many aspiring surgeons stand in some hero-worship of a great surgeon doing these colostomies. Very few hospitals, even in this city, are equipped to carry on such major surgery. These men watching the procedure and feeling that it is the recognized treatment of carcinoma of the cervix are going back to their suburban hospitals and attempt to do the operation, without being able to get sufficient blood while the patient is on the operating table. I think while it is a bad experiment, it is worthy of trial because it is done in unselected cases and the over-all figure will be an unqualified one."

DR. STENNING (Sydney, Australia).—Cancer of the cervix has been occupying our attention for a long time, and Dr. Slinck and Dr. Twig have been pioneers in doing the Wertheim operation at the hospital where I happen to be. I say that, actually, we feel our results in the treatment of carcinoma of the cervix compare favorably to those we have read about which have been reported in other parts of the world. They had been doing the Wertheim operation since 1927 and had already published a series of cases covering ten-year cures for the period 1930 to 1940, and it is anticipated that they will soon publish the fifteen-year cures.

"In our clinic we have always felt that it is rather difficult to estimate the stage of carcinoma and, furthermore, we feel that carcinoma should be subjected to radium treatment preliminarily and, if it then becomes favorable, to submit it to the Wertheim operation.

"We feel that by putting radium in at the beginning we take a lot of patients away from trouble because we find in some cases that the disease regresses. We don't rely entirely on what the outside world believes in regard to uterine cancer because we find some of them regress when we might have thought them radioresistant. We give the patients 7,200 milligram hours spread over a period of about five days, at the end of that time the radium is removed and then, five weeks later, if the patient is considered operable, operation is done. Prior to the war, the operative mortality was 15 per cent. Since the war period, however, with the

advent of antibiotics, chemotherapy, and blood transfusion the corrected mortality is about 5 per cent of all cases. Since the war we feel with the help of these adjuvants that the Wertheim operation is not one that carries with it such a high mortality and that it is capable of further improvement."

I feel that the Wertheim operation is one which involves teamwork and we like to use teams especially trained in its performance.

DR. NELSON B. SACKETT.—Referring to one of the main contentions of the proponents of surgery, Dr. Sackett stated that some years ago, at the Woman's Hospital, he studied about 900 cases, of which "359 were available for ten-year statistics. Without corrections for any cause whatsoever, the irreducible figures indicated that if a patient survived 5 years she would have a 75 per cent chance of being alive at the end of 10 years. A patient rarely died after surviving 10 years." This survey was made about 1937 upon cases who had received what is now considered inadequate primary radiation. With adequate irradiation five year survivors have over 85 per cent chance of living ten years or more.

"We have not been doing lymphadenectomy; but it should be done in cases where the local lesion has responded well."

Referring to the "criteria of Heymann, of Stockholm, or the League of Nations classification," Dr. Sackett stated that "where there is some doubt about the grouping of cases, they are always placed in the less advanced Stage."

In cases in which there is parametrial infiltration and one cannot decide whether it is malignant or not, if it clears up under radiation it is probably carcinoma; but if it fails to improve by this therapy or gets worse, it is probably inflammatory. That is a valuable point in determining the League of Nations stage.

After referring to one of the main contentions of the proponents of surgery, Dr. Sackett stated that some years ago, at the Woman's Hospital, he studied about 800 cases, of which "only 300 were available for ten-year statistics, and without any deductions or corrections for any cause whatsoever, the irreducible figures indicated that if a patient survived five years she would have well over a 75 per cent chance of being alive at the end of 10 years; that some died between five and ten years and a few died after the lapse of ten years." This survey was made about 1935, the doctor said, in the era of what is now known to be that of intractable primary radiation, as it sounded to the Reporter. Continuing his remarks, Dr. Sackett said:

"We have not been doing lymphadenectomy."

After a few further remarks, the doctor stated that their present figures indicate an increase in the survival rate in these cases if they were to eliminate intercurrent deaths, such as heart failure and various other causes, and that under these circumstances the survival rate would be well over 70 per cent and possibly close to 80 per cent.

Referring to the "criteria of Heymann, of Stockholm, or the League of Nations classification," Dr. Sackett stated that "where there is some doubt about the grouping of cases, they are always placed in the less advanced category."

After referring to two cases that they have in the hospital at the present time, both of which presented palpable glandular involvement, one of which it was possible to subject to preliminary x-ray therapy, and the other of which was not suitable for primary radiation, Dr. Sackett concluded his remarks as follows:

"Heymann states that in cases in which there is infiltration if one cannot decide whether it is malignant or not, if it clears up under radiation it is probably carcinoma, and if it fails of improvement by this therapy or gets worse, it is probably inflammatory. I think that is a valuable point in classifying these cases."

DR. WILLIAM CRAWFORD WHITE.—I have seen some of the ill-effects of irradiation. Moreover, I am very much interested in the fact that Dr. Taylor is talking about more and more surgery. I wonder how many cancer cells he is going to sweep around the peritoneal

cavity (unwittingly, of course) when he does that operation. Objectively, I think it is a factor that most of us are not fully aware of. I have definitely demonstrated in breast surgery that there are plenty of cancer cells in the washings from our gloves after operation. I believe there are many cells which are distributed about in the wound at the time of operation. I think that must be borne in mind (in considering surgery) versus radiation where there is a great deal of fibrous encystment and retardation of growth.

"There is another factor which I do not understand, but which, nevertheless, is a factor, and that is, when there is metastasis it may lie dormant for varying periods of time; then something happens which causes the cells to grow again. Therefore, as long as the patient lives she may start to grow cancer again. I know that in my personal experience I have seen patients who have lived, thirteen, fifteen, and even seventeen years and at the end of that time start to grow cancer again, despite the fact that they had been in perfect health in the interval.

DR. READ (Closing).—"My first thought, I frankly admit, was that I would be hung, drawn, and quartered by the deep x-ray therapists because I thought I might provoke some discussion on their part or, rather some disagreement with the views I advanced, and I find that such an exponent of this method of treatment as Dr. Corseaden has more or less agreed that x-ray radiation does not adequately radiate the pelvic lymph nodes.

"I was interested in Dr. Healy's statement that in his hands adenocarcinoma cases showed almost as good results as the squamous celled group. However, that has not been our experience. Whether we are faulty in our technic of radium application or not I cannot say, but I do not think that any clinic in England which has taken the trouble to analyze the adenocarcinoma cases and contrast them with squamous epitheliomas, show any results comparable to those obtained by radiation in the squamous celled group.

"To Dr. Taylor I would say that a large number of people would probably prefer operative interference to the exclusion of every other means of treatment, but it must be remembered that this evolution in our Hospital has come about after having had extensive experience with the radical operation as a routine method of treatment in all cases. In respect of operative possibilities in Stage III cases you cannot get away from the fact that the clearance in Stage III cases is not a very wide one." This is borne out by the results, and as expected the surgical results are worse in Stage III than in Stages I and II cases. You cannot escape the fact that Stages I and II growths give the best results radiotherapeutically, so I feel until some better results are shown by surgery it is best to be conservative and treat these cases radiotherapeutically except in those instances in which radioresistance is proved, and that is an important point.

"Radioresistant cases fall into three classes: one, where the cervix fails to heal; two, where it heals and then later breaks down and thirdly where at a still later date biopsy shows persistence of continuous activity. When I speak of repeated biopsies I refer to instances of radioresistance where active growth is shown three, four or six months later; that is, active growth present in the cervix three months or six months later. In one of my cases active growth was present 14 months after radiation.

"I agree with the difficulty of classification. As a matter of fact, about 60 per cent of my lymphnode dissections resulted from misinterpretation of the type of disease with which I was dealing. I remove the appendages in these cases in which the lymph nodes are extirpated and it is from such cases that I obtain the greater proportion of material.

"Dr. Corseaden mentioned the question of remote gland involvement. That is an important and interesting point. I did not mention it here, but for years in those of Mr. Bonney's cases subjected to the radical operation and who died, at autopsy, it was remarkably rare that remote nodes were found in cases that were clinically operable. Some are found in the region of the celiac axis vessels but, generally speaking, in the Wertheim operation a complete gland clearance begins at the bifurcation of the aorta, and if this is free you can skin the glands completely from the bifurcation downwards. It is not always the case that remote glands are not involved and I can cite two cases of clinically Stage I growths with metastatic involvement of the supraclavicular gland group.

In respect to Dr. Smith's discussion, I think there is some slight mistake on Dr. Smith's interpretation of what I said. In 45 of the 54 patients who were subjected to operation there was proved radioresistance, and these were doomed to death because biopsy showed active growth with break-down of the initially-healed cervix. The remaining 9, a small proportion, came into the groups I mentioned, such as pregnancy, stenosis of the vaginal vault, and the others conformed to the other categories.

"I agree with Dr. Taylor on the question of the advanced growth. It is a difficult problem, and a matter of conscience on the part of the surgeon. Whether he does ultraradical surgery involving cystectomy or partial colectomy in addition to radical hysterectomy depends on the attitude of the patient herself. In other words, if the growth is so advanced that you cannot effect a cure radiotherapeutically and the alternative is certain death, certain patients will say, 'I leave it to your judgment.' The results can only be assessed on the basis of a large number of cases and, as far as I know, this has not been done. But there is the other factor: Is the patient more comfortable after extremely radical surgery than she is following radiation? I cannot answer that question for the reason that I have not had a sufficiently large experience of such cases.

"It was interesting to hear Dr. Stenning of Sydney, Australia, say that they are still doing the Wertheim operation as the method of selection. Actually, if you work it out over a series of figures, you will find that, roughly, 30 to 31 per cent of all patients presenting are alive at the end of five years whether treated by radiation or by surgery. I think if you combine surgery with radiation, in selected cases, you can get that survival rate up.

"I am not enough of a mathematical genius to figure out what Dr. Sackett had in mind, but as I understood him he said that when a patient lives five years after radiation she has a .75 per cent chance of living five years longer and a 25 per cent chance of dying within the next 5 years."

## NEWER CONCEPTS OF MENSTRUATION\*

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BLEEDING is the most striking feature of the menstrual process. A large part of the clinical and laboratory study of menstruation in the past two decades has, therefore, been directed toward the blood vessels of the endometrium. On the basis of this work, an explanation of cyclic uterine bleeding as a consequence of alterations of the coiled arterioles of the endometrium has gained widespread acceptance. Unfortunately, this explanation has been carried so far that it now fits only certain special cases. The most recent laboratory findings as well as many familiar clinical observations require a return to a more general physiologic concept of menstruation as a result of withdrawal of metabolic support of the endometrium.

It has been known for some time that the vasculature of the endometrium undergoes cyclic changes along with the glands and stroma (Saito,<sup>22</sup> Daron<sup>5</sup>). The basal arterioles, situated in the deepest portion of the endometrium, are not shed in the menstrual discharge and do not participate in these cyclic changes. The coiled arterioles, which eventually reach almost to the superficial epithelium, manifest remarkable alterations. Just after the completion of bleeding, the endometrium is shallow and the coiled arterioles have but a few loops. As the follicular phase proceeds, the endometrium thickens and the arterioles add loops and lengthen, remaining confined to the inner half of the mucous membrane. If ovulation fails to occur and growth continues, due to continued estrogen stimulation, vessels such as those in Figs. 1, 6, and 7 develop. If, however, a functioning corpus luteum is formed, the coiled arterioles become much more complex and extend further out into the endometrium as the secretory changes of the glands and stroma take place. With the approach of menstruation, the contortion and buckling of the vessels become extreme, as in Figs. 2, 8, and 9. The distal portion of the vessel is lost thereafter in the menstrual discharge. Markee<sup>15</sup> has added greatly to the understanding of these changes by describing them as they take place in endometrium transplanted to the anterior chamber of a rhesus monkey's eye. He observed that the bulk of endometrial bleeding is arteriolar in origin and that, therefore, the coiled arterioles control the amount and rate of menstrual hemorrhage. The explanation of menstruation as a consequence of vascular changes is based primarily on these observations.

In the years that have followed the publication of these findings, so many interpretations of their meaning, all of them similar, have been made in textbook and monograph discussions of menstruation that it would be unfair to cite any one author's exposition of the vascular hypothesis. It is restated here without citation, therefore, in its two basic forms, with the awareness that the separation between them is academic.

\*Presented before the Obstetrical and Gynecological Section of the Baltimore City Medical Society, Feb. 13, 1948.

The first, a mechanical concept, is based on the observations that the coiled arterioles increase rapidly in complexity and extent as the secretory phase of the cycle progresses. This increasing complexity is supposed to reach a point at which it impedes the flow of blood to the endometrium, producing ischemia,

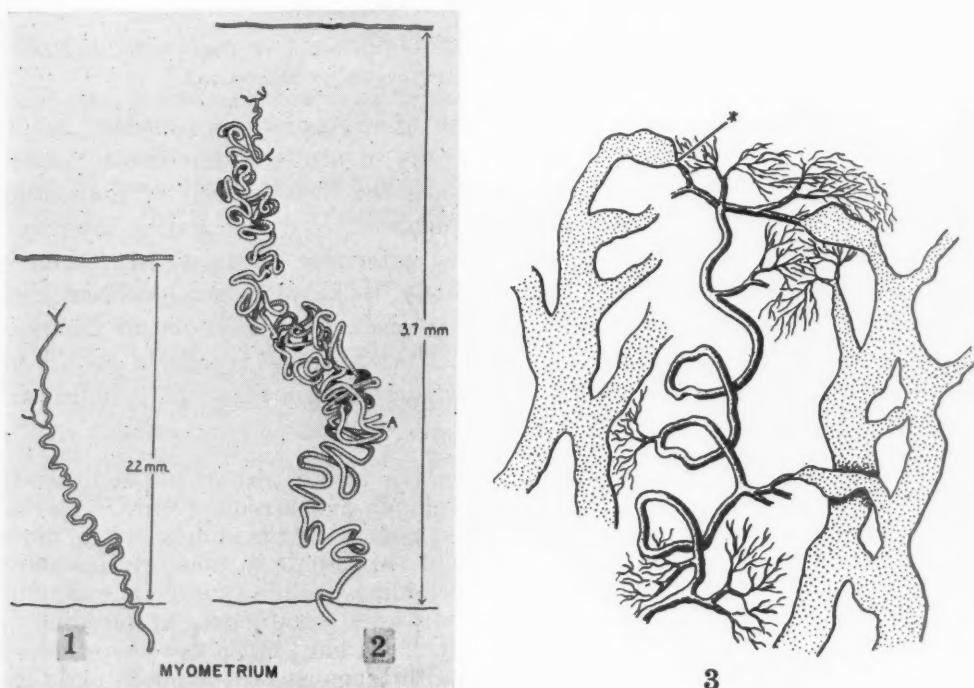


Fig. 1.—Projection reconstruction ( $\times 20$ ) of the lumen of a coiled arteriole on the twenty-sixth day of an anovulatory cycle. One ovary contained a large cystic follicle. By this stage the vessel of an anovulatory cycle is usually more complex than this, as may be seen in Figs. 6 and 7. The simplicity of this vessel, as compared with that in Fig. 2, is striking and somewhat overstates the case. Reproduced from Daron, Am. J. Anat. 58: 405, 1936, Fig. 9.

Fig. 2.—Projection reconstruction ( $\times 20$ ) of the lumen of a coiled arteriole on the thirtieth day of an ovulatory cycle. Branching occurs at A but only one branch has been reconstructed. Note the complexity of this vessel and compare with Figs. 8 and 9, which illustrates a similar vessel, on the first day of menstruation. The contrast with Fig. 1 requires no comment. Reproduced from Daron, Am. J. Anat. 58: 403, 1936, Fig. 5.

Fig. 3.—Schlegel's sketch of endometrial vasculature of the human uterus as seen in injected material. The coiled arteriole ascends between two large columns of veins. At the asterisk and at two other places arteriovenous anastomoses are indicated. This is a highly diagrammatic representation. Reproduced from Schlegel, Nord. Med. 24: 2061, 1947, Fig. 2.

which then sets off the chain reaction of menstruation. The other, a pharmacodynamic concept, stems from the observation that prolonged periods of vasoconstriction are invariable precursors of the other menstrual changes. The growth and differentiation of the coiled arterioles are presumed to render them sensitive to the action of vasomotor substances. These then produce vasoconstriction, ischemia, and menstruation. Both concepts assume that continued growth of a complex coiled arteriole is a necessary precursor of menstruation. In this sense, the hypothesis of a vascular basis of menstruation as stated by many authors, compounded freely of ideas from both of the concepts stated

above, bypasses and even contradicts the earlier work on hormone withdrawal as the common precursor of menstrual flow. As will be discussed below, such a conclusion is quite erroneous.

A new factor in this vascular explanation has been introduced by the recent observations of arteriovenous anastomoses in human endometrium.

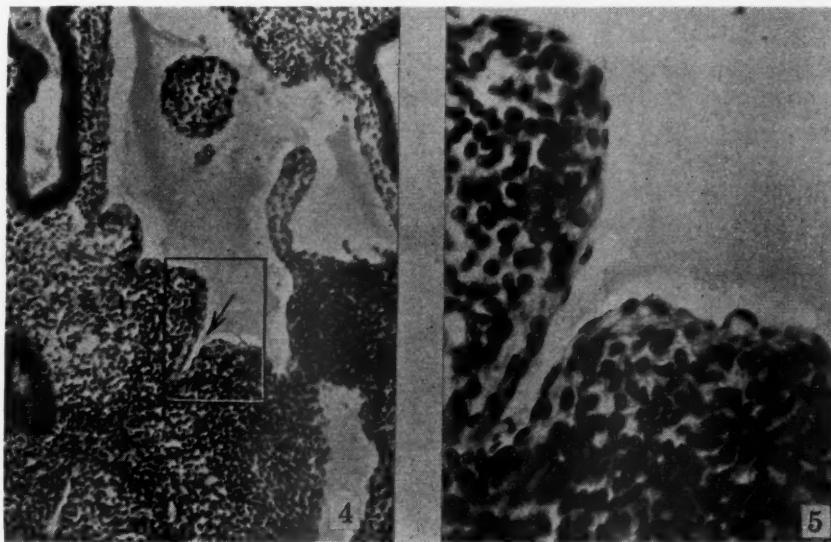
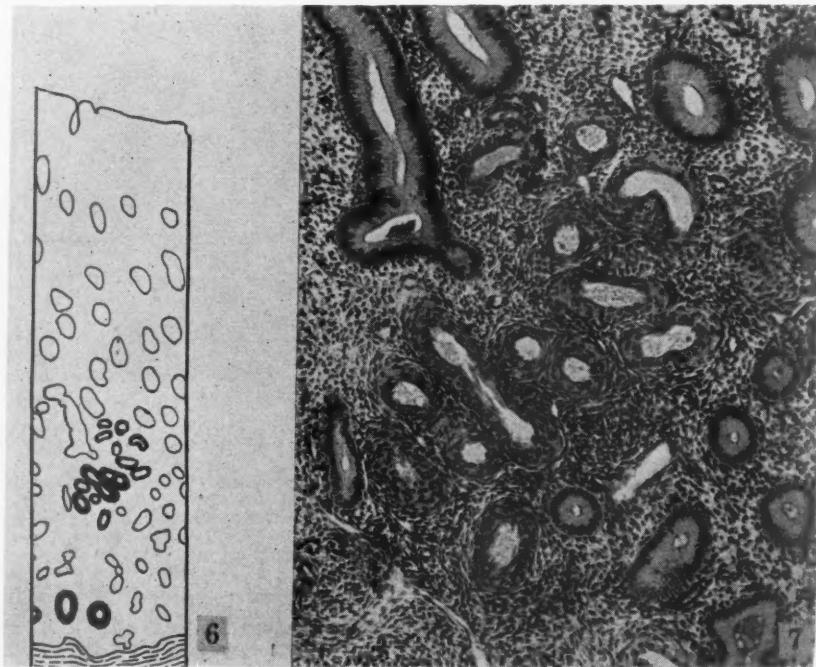


Fig. 4.—Section of human endometrium ( $\times 90$ ). A large venous lake and several glands may be seen. At the arrow, an arteriole enters the venous lake. Reproduced from Schlegel, Nord. Med. 24: 2067, 1947, Fig. 10.

Fig. 5.—Detail of Fig. 4 ( $\times 360$ ). At this magnification, the identification of the vessel entering the venous lake is by no means as definite as at the lower magnification, although some detail is undoubtedly lost in photography. Reproduced from Schlegel, Nord. Med. 24: 2066, 1947, Fig. 9.

Dalgaard<sup>4</sup> and Schlegel<sup>23</sup> have independently reported the presence of shunts between the branches of coiled arterioles and venous lakes of the functional zone. As described by Daron,<sup>6</sup> these venous lakes are dilated venules which appear shortly before menstruation in the middle third of the endometrium. Schlegel's sketch of these vessels is reproduced in Fig. 3. His first observation of anastomoses was made in human uteri injected with colored substances under high pressures. Under the microscope, after sectioning the uteri, Schlegel was able to see points where his red arterial injection mass met the blue venous material without the intervention of a capillary bed. Dalgaard, who injected India ink into the arteries, found large numbers of ink particles in the venous lakes. Both authors were later able to find the anastomoses in uninjected histologic preparations. One such anastomosis is shown in Figs. 4 and 5, which are made from Schlegel's original photographs. Schlegel and Dalgaard agree that these shunts occur with increased frequency in the secretory phase of the menstrual cycle. Schlegel suggests that eventually so much of the arterial blood is shunted into the venous system that a capillary ischemia results. This then precipitates endometrial breakdown and menstruation. He also argues that the presence of arteriovenous anastomoses provides an ideal vasculature for the establishment of placental circulation.

The existence of these shunts cannot be accepted without reservations. Bartelmez<sup>1</sup> has reported his inability to find anastomoses in the endometrium of the rhesus monkey, but this may be a species difference. The very high pressures employed by Schlegel and Dalgaard for injection raise a question about the production of artefacts. It is certainly difficult to make a positive identification of so small a vessel as that seen in Figs. 4 and 5 as arteriolar. Serial sections of endometrium are required to prove the presence of these arteriovenous anastomoses conclusively. Nevertheless, the fact that these structures have been observed independently by two workers makes subsequent confirmation appear likely. Schlegel<sup>24</sup> has recently reported clinical studies of the effect of ephedrine on dysmenorrhea, based upon the possible vasomotor action of this drug on the arteriovenous anastomoses.



**Fig. 6.**—Outline drawing of a section of endometrium of the rhesus monkey ( $\times 25$ ) on the twenty-eighth day of an anovulatory cycle. This and Fig. 8 were made by printing photographs of these sections and then drawing in the outlines of the superficial epithelium, glands and arterioles. The myometrium was sketched in schematically. The photograph was then bleached out. The arteriolar field is restricted to the inner half of the endometrium and is relatively simple as compared with Fig. 8. Reproduced from Kaiser, Anat. Rec. 99: 215, 1947, Fig. 6, with changes.

**Fig. 7.**—Photograph of the arteriolar field in Fig. 6 ( $\times 100$ ). The vessel walls are compact and eosinophilic. Reproduced from Kaiser, Anat. Rec. 99: 221, 1947, Fig. 14.

It is difficult to explain the amenorrhea of early pregnancy by the current hypothesis of a vascular mechanism for the initiation of menstruation. Although no special study has been devoted to this matter, it appears reasonable to assume that the coiled arterioles of the endometrium in the relatively vast area removed from the site of implantation differentiate to the same extent as those of the nonpregnant uterus, at least in the first fourteen days after ovulation. The same assumption may be made in reference to arteriovenous anastomoses.

Nevertheless, bleeding does not usually occur in the pregnant animal. Schlegel attempts to account for this by postulating a special local effect of chorionic gonadotropin which increases the "irrigation coefficient" of the capillary bed and thus prevents anoxemia.

There are still other objections to the vascular explanation. It has been repeatedly observed that the coiled arterioles found in the presence of ovulatory menstruation differ considerably from those seen during anovulatory bleeding.<sup>12</sup> Despite this fact, the clinically observed bleeding is identical in the two conditions by all our present criteria. The major differences in the appearance of coiled arterioles of the rhesus monkey in these two circumstances are shown in Figs. 1, 2, 6, 7, 8, and 9. Figs. 6 and 7 depict the typical appearance of a coiled arteriole on the twenty-eighth day of an anovulatory cycle. They demonstrate maximum anovulatory growth. In contrast, Figs. 8 and 9 show the vessels

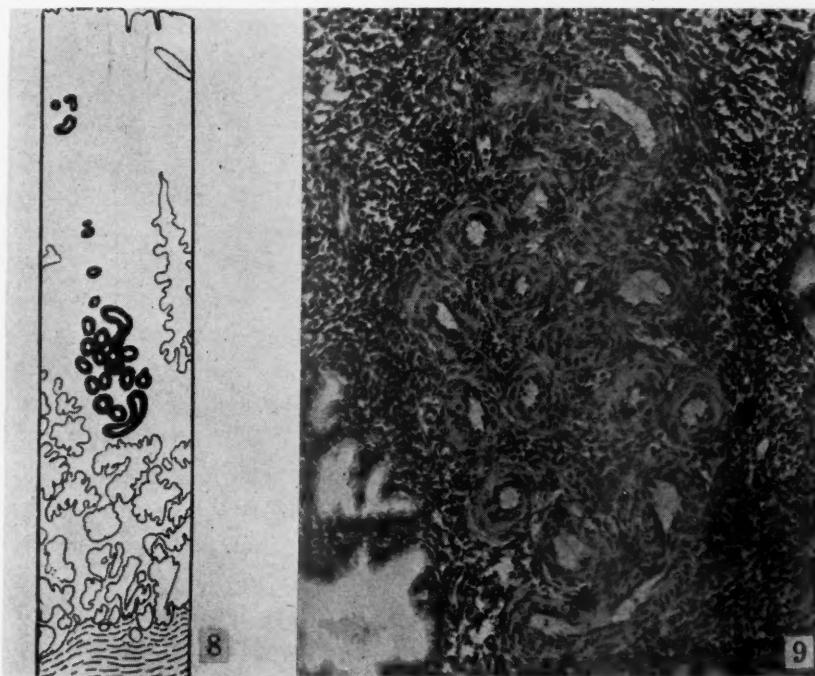


Fig. 8.—Outline drawing of a section of endometrium of the rhesus monkey ( $\times 25$ ) on the first day of ovulatory menstruation. The arteriolar field is in the middle of the endometrium and branches are seen extending well out toward the superficial epithelium. The field is more complex than in Fig. 6. Reproduced from Kaiser, *Anat. Rec.* 99: 215, 1947, Fig. 1.

Fig. 9.—Photograph of the arteriolar field in Fig. 8 ( $\times 100$ ). The arteriolar walls are swollen and much less eosinophilic than these in Fig. 7. Reproduced from Kaiser, *Anat. Rec.* 99: 217, 1947, Fig. 9.

in the endometrium at the onset of menstruation in an ovulatory cycle. Comparing Figs. 1 and 2, and 4 and 6, it can be seen that the vessel of ovulatory menstruation is larger, more complex, and reaches further out toward the superficial epithelium. Its area of greatest coiling is in the middle third of the endometrium. In Figs. 7 and 9, higher magnification reveals that the vessel walls in ovulatory cycles are thicker and stain less deeply. These differences

are known to be an effect of progesterone. Detailed studies with cytochemical techniques are required to prove their functional significance. It must be remembered that bleeding can and does occur from an endometrium with a much simpler arteriolar bed than these. Such is the case in bleeding following oophorectomy or spinal cord transection done at the midinterval, for example. Although no study has been made of this subject, coiled arterioles are not conspicuous in the presence of endometrial hyperplasia, despite the bleeding with which this condition is associated. Finally, there is suggestive evidence that bleeding can occur in the rhesus monkey under experimental conditions without any proliferation of coiled arterioles at all (Kaiser<sup>14</sup>).

Menstruation, at least in the form of microscopic cyclic bleeding in the absence of coiled arterioles, has recently been shown by Kaiser<sup>13</sup> to be the normal condition in the New World monkeys. These animals, which are closely related anthropologically to the other Simiae, including the rhesus monkey and man, were long believed not to menstruate. However, more detailed studies by Goodman and Wislocki,<sup>8</sup> and Hamlett,<sup>9</sup> using daily vaginal lavage, have revealed cyclic uterine bleeding of microscopic proportions in the New World species. The endometrium of these platyrhine monkeys goes through a cycle much like that of the rhesus and the human being (Dempsey<sup>7</sup>). Despite this, a special study of the vasculature of the platyrhine endometrium has demonstrated that there are no coiled arterioles present. Instead, there is a very simple system of small arterioles which run through the endometrium almost without contortion after branching once or twice in the basalis. These vessels do not appear to undergo any cyclic alterations. Two of them may be seen at the arrows in Fig. 10. This illustration depicts the appearance of ovulatory menstruation in the endometrium of a capuchin monkey. The contrast between the arterioles in Figs. 7 and 9 and those in Fig. 10 does not require emphasis.

These observations indicate that the current explanation of menstruation based upon alterations of the coiled arterioles fails to account for much that is known about the menstrual process. Before a vascular explanation can be abandoned, more information is needed concerning the contraction cones described by Daron.<sup>5</sup> He pointed out that the arcuate arteries of the myometrium traverse the muscle parallel to the serosal surface and give rise to the radial arteries which run at right angles to it. These then travel toward the uterine cavity and divide into two types of vessels. One type enters the endometrium to become a basal arteriole, the other to become a coiled arteriole. In several menstruating uteri, Daron observed that the radial arteries which led to coiled arterioles are constricted so as to form a cone of contraction in the zone of myometrium adjacent to the endometrium. This may be seen strikingly in Fig. 11, from Daron's original preparation. It is clear that such a constriction would effectively occlude the blood supply of the endometrium. Okkels and Engle<sup>16</sup> and Hasner,<sup>10</sup> who have described the microscopic structure of the myometrial radial arteries and their branches have unfortunately not discussed this phenomenon. Indeed, Okkels and Engle appear to describe contractile tissue only in the walls of the basal arterioles. If, however, there are structures

capable of occluding blood supply to the vessels which supply the spongiosa and functionalis, then a simple vascular explanation of menstruation may be possible regardless of the presence or absence of coiled arterioles.

It may be noted here that the sole study of lymphatic channels of the endometrium of the rhesus monkey has indicated that lymphatics are absent from the spongiosa and functionalis.<sup>27</sup> Hence menstruation may be in part due to an inadequate mechanism for the resorption of tissue breakdown products following the cessation of metabolic support. Reynolds<sup>21</sup> has recently discussed this matter in more detail.

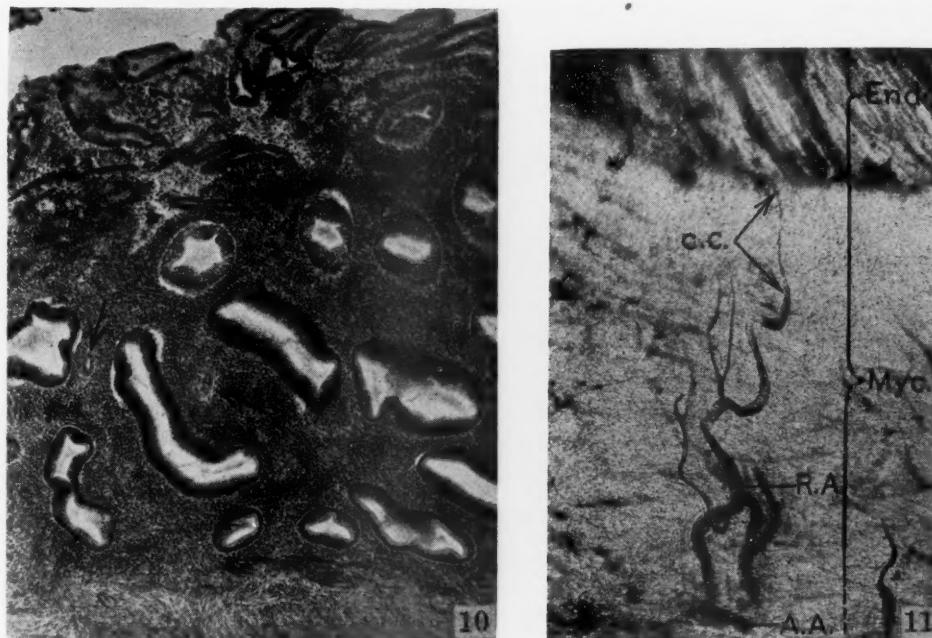


Fig. 10.—The endometrium of a menstruating capuchin monkey ( $\times 40$ ). There is disorganized debris in the lumen with a large amount of leucocytic infiltration but not much destruction of the epithelium. The more superficial glands manifest evidence of progestational changes. Two medium-sized arterioles (c. 40-50 microns) are seen at the arrow. Reproduced from Kaiser, Anat. Rec. 99: 367, 1947, Fig. 4.

Fig. 11.—Photograph ( $\times 34$ ) of a cross section, 0.2 mm. thick, of the uterus of a rhesus monkey on the second day of the menstrual phase of an anovulatory cycle. The myometrial arcuate artery (A.A.) in the vascular stratum of the myometrium (Myo) gives rise to a myometrial radial artery (R.A.). This vessel in turn enters the endometrium (Endo) at the arrow, to form a coiled arteriole. In the inner fifth of the myometrium, the radial artery is tightly constricted. This is the contraction cone (C.C.) of Daron. This is a previously unpublished photograph of material from Daron's animal No. 113.

#### Influence of Past Cycles on Endometrium

A most significant contribution to the understanding of abnormalities of menstruation has recently been made by Phelps as a culmination of a series of studies<sup>3, 17, 18, 19</sup> in the Department of Obstetrics and Gynecology of Vanderbilt University Medical School. These have followed the observation by Zuckerman<sup>28</sup> that the effect of a single dose of estrogen on the monkey is affected by its response to and distance in time from previous estrogen stimulation. Phelps<sup>19</sup> has now directed attention to the factor of previous treatment in the production of menstrual disorders in the rhesus monkey. She states that:

"... any given episode of uterine bleeding is . . . influenced by the components, relative strength and duration of action of hormonal stimuli acting prior to application of the current stimulus. In other words, the influence of a single course of stimulation by ovarian hormones is not limited to the cycle which that course of stimulation represents. Its influence extends through at least one subsequent cycle and probably through more than one. This influence upon subsequent cycles is mediated at least in part through the structural changes produced in the endometrial vascular bed. These changes may be transient or permanent, i.e., carried over into the next cycle. The specific vascular architecture existing at the beginning of any single cycle has an important influence upon the duration of the uterine bleeding in that cycle."

It is evident from this that to function normally the epithelium, stroma, and blood vessels must develop simultaneously to the same level of functional capacity. It is not enough that the epithelium alone develops. Hertig's essay<sup>11</sup> on the endometrium during the human cycle unfortunately does not include sufficiently correlated reference to the arterioles. A correlated study of endometrium and arterioles throughout the cycle in the human being would provide a base line with which the endometria of abnormal reproductive cycles could be compared.

It has long been assumed that if the ovary forms a corpus luteum, all the necessary events for successful implantation inevitably follow. There is, however, little reason to assume that every corpus luteum which forms reaches the level of hormone production necessary for the coordinated growth of all endometrial structures. Certainly there must on occasion be a failure to form a functioning corpus luteum. Under these circumstances, endometrial growth, and the growth of coiled arterioles in those species in which they are present, does not proceed to its fullest extent. This, in turn, as Phelps emphasizes, sets the stage for further endometrial anomalies in later cycles. Brewer and Jones,<sup>2</sup> discussing corpus luteum-endometrium relationships, point out that there is considerable variation, especially at the end of the cycle. They report one case in which an apparently normal corpus luteum was associated with endometrium which showed no evidence of past or present secretory activity. They surmise that this reflects either failure of the corpus luteum to function or failure of the endometrium to respond. They also point out that these variations are quite common.

The observation of the activity of endometrial epithelium on one occasion, or the determination of hormone levels in one cycle would, therefore, appear to be only the start of a thorough investigation of menstrual abnormalities. Before a therapeutic regime directed at the correction of infertility on the basis of menstrual abnormalities can be declared a success, all the elements of the endometrium, the epithelium, the stroma, and the blood vessels, must have returned to normal. At present, it can be suggested that certain kinds of incoordinate growth of these three elements may be related to certain types of functional abnormality. If this be the case, endometrial biopsy should prove to be of increasing value as an index of therapy.

#### Discussion

Menstruation is but one phase of a continually varying cycle of growth and regression. It is the period of return to a resting condition of an endometrium

which has undergone a period of growth. Once endometrial growth has occurred, a steady supply of metabolites, increased over that required for the resting state, must be maintained if regression is to be prevented. Further, the metabolites must be supplied in ever increasing quantities if continued growth is to occur. The steroid sex hormones provide the growth stimulus to the endometrium and thereby regulate its metabolic needs and participate in its metabolic support. When metabolic support is withdrawn, regression begins. This statement is true for all mammals.

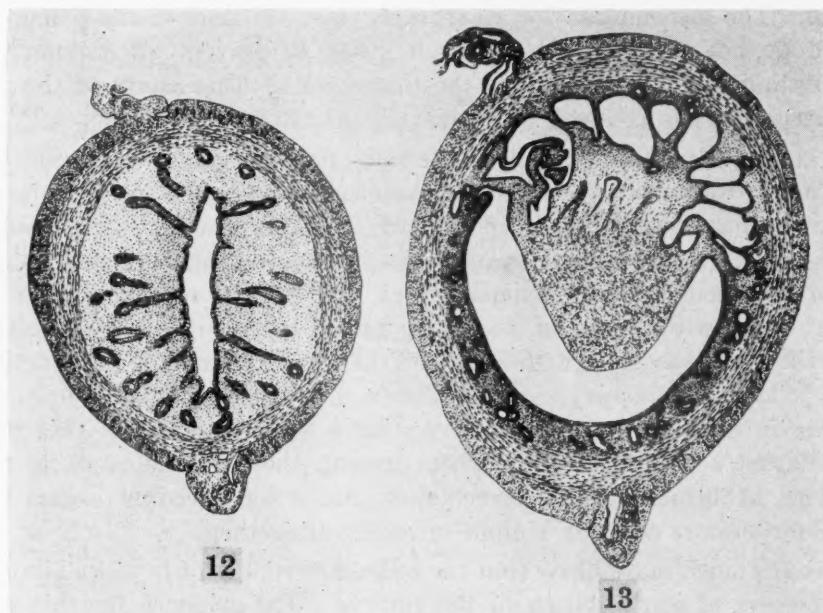


Fig. 12.—Transverse section of a uterine horn of the South African elephant shrew, *Elephantulus myurus* ( $\times 25$ ). This animal has recently ovulated. The mesometrial border is at the top. The two layers of myometrium can be readily made out. The glands and stroma are uniform in appearance throughout the circumference of the horn. Reproduced from van der Horst and Gillman, South African J. M. Sc. 6: 1941, Fig. 3.

Fig. 13.—Transverse section of a uterine horn ( $\times 25$ ) of the elephant shrew showing a large endometrial polyp. This is the normal state when ovulation is not followed by implantation. The polyp always develops on the mesometrial side. The uterine glands beneath it are dilated, while those elsewhere are small. The stroma away from the polyp is dense and compact, while between the polyp and the dilated glands remnants of stromal edema can be seen. The polyp itself has undergone necrosis, although the covering epithelium is still intact as a very thin layer not visible at this magnification. It is immediately following this stage that bleeding occurs from the necrotic area. Reproduced from van der Horst and Gillman, South African J. M. Sc. 6: 1941, Fig. 12.

Why, then, do only certain primates menstruate? There are two major clues to an answer. Van der Horst and Gilman<sup>25, 26</sup> have observed cyclic uterine bleeding in the South African elephant shrew which is classed by most taxonomists as a rodent. The endometrium of this animal responds to progesterone by forming a large endometrial polyp, almost a deciduoma. This polyp grows until, at the end of the cycle, it undergoes necrosis, hemorrhage, and desquamation. This may be seen in Figs. 12 and 13. It appears that this remarkable growth exceeds the capacity of the uterus for resorption of tissue and tissue-breakdown products. This is in all likelihood also true of the primate endometrium. There are no lymphatic channels present to provide ready egress for

the catabolites formed following withdrawal of metabolic support. They remain in situ and cause further tissue destruction until the endometrium is shed down to the area maintained by the capillary bed of basal arterioles.

The other major clue is Markee's observation<sup>15</sup> that regression in the rhesus monkey is not necessarily followed by menstruation provided that it proceeds slowly. By withdrawing estrogens gradually over a long period of time, he was able to produce transition from full growth to a resting state without necrosis, hemorrhage, or desquamation. The factor of time is, therefore, of crucial importance. The mechanisms for resorption which do exist in the primate endometrium do not operate with sufficient speed to prevent an accumulation of toxic substances which is lethal to the tissue itself. This aspect of the problem of menstruation has received but a fraction of the study it deserves.

It is unlikely that the coiled arterioles play any significant role in these basic events. Kaiser has described the absence of such vessels in the endometrium of menstruating New World monkeys. He has also observed their almost complete absence in the endometrium of rhesus monkeys which have received massive doses of estrogens. Other animals given the same doses manifested uterine bleeding upon withdrawal of the hormone. Finally, it has been repeatedly observed in the macaque that there are no differences in uterine bleeding between ovulatory and anovulatory cycles. The major differences between the coiled arterioles in these two kinds of cycles have been discussed. This does not refute Markee's conclusion that, when present, these arterioles act to regulate the extent of hemorrhage. Nevertheless, menstrual bleeding occurs whether coiled arterioles are complex, simple, or absent altogether.

It seems much more likely that the coiled arteriole is of principal importance in the process of implantation of the embryo. The evidence for this is as yet only indirect. Ramsey has made a beginning in her study of the changes of the endometrial vasculature during pregnancy in the rhesus monkey.<sup>20</sup> Phelps has produced evidence that menstrual irregularities are associated with anomalous growth of the coiled arterioles in rhesus. This may therefore offer further explanation of the relative sterility of women with menstrual irregularities. Phelps' other observation, that the effects of hormone administration are dependent at least in part on the previous hormonal history of the subject as reflected in the state of the coiled arterioles, has very broad implications in the study of sterility. Some of these have been suggested. The further investigation of the association of the coiled arterioles with the implantation of the fertilized ovum, especially in the light of this anamnestic vascular phenomenon described by Phelps, can be expected to yield results of great experimental and clinical interest.

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## LEIOMYOSARCOMA OF THE UTERUS\*

Report of 16 Cases, 1917 to 1948

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A RECENT unusual incidence of leiomyosarcoma of the uterus (four case specimens in six and one-half months) observed in our pathologic laboratory has stimulated interest in reviewing the cases of this unusual neoplasm. Unhappily, the correct diagnosis is rarely made, or even considered, at the operating table due to the low incidence and the extreme difficulty in gross pathologic diagnosis. At the Methodist Hospital, we were able to find only 16 clear-cut cases of leiomyosarcoma in a thirty-year survey ranging from Jan. 1, 1917, to Jan. 1, 1948. During this same period, 2,318 benign leiomyomas and 40,382 general pathologic case specimens were examined. The ratio of leiomyosarcomas to leiomyomas was approximately 1 in 145, or 0.69 per cent, and to the general specimens 1 in 2,524, or 0.04 per cent.

TABLE I. INCIDENCE OF SARCOMA UTERI

	SARCOMAS	LEIOMYOMAS	INCIDENCE (PER CENT)
Evans <sup>7</sup>	13	3,297	0.39
Pemberton <sup>12</sup>	14	2,991	0.46
Meigs <sup>10</sup>	9	1,330	0.68
Novak and Anderson <sup>1</sup>	59	6,981	0.84
Kelly and Cullen <sup>13</sup>	17	1,400	1.2
Kimbrough <sup>2</sup>	43	3,338	1.3
Bosse and Stanton <sup>6</sup>	27	not given	"approximately 2.0"
Davis, Howe, and French	16	2,318	0.69

Table I shows that our percentage incidence of leiomyosarcomas to leiomyomas is comparable to the rate in other larger series of uterine sarcoma. It is of note that our group contained no instances of endometrial sarcoma, or sarcoma botryoides.

In the last twelve months of this study we have segregated the cellular leiomyomas from the usual type. Twenty-five of 223 leiomyomas, approximately 1 in 9, were found to be in this category, an incidence of 11.2 percent.

We have tried to analyze this 16 case series from a clinical, operative and pathological point of view with an eye to clarifying, as far as possible, the criteria for diagnosis at the operating table and under the microscope. The survival rate is correlated with the operative procedure, the degree of malignancy, and the recurrence incidence found in each case. Two general

\*Read, by invitation, at a meeting of the New York Obstetrical Society, Oct. 14, 1947.

grades of malignancy are noted: the first, unequivocal leiomyosarcoma, and the second, low-grade leiomyosarcoma.

**Gross Criteria.**—The gross characteristics of the tumors as detailed in the operative notes and the pathologic descriptions were analyzed, particularly with relation to distinguishing them from leiomyomas. The results are shown in Table II.

TABLE II. GROSS APPEARANCE OF LEIOMYOSARCOMAS (16 CASES)

	NO. OF CASES
Grossly indistinguishable from leiomyoma	2
Consistency different from leiomyoma	14
A. Soft and necrotic	11
B. Friable and granular	3
Color different from leiomyoma	7
Loss of fasciculation	10
Gross evidence of invasiveness	2

From Table II, it appears that in 14 of the 16 cases there were gross characteristics of the tumor which might help to distinguish it from the common leiomyoma. It is true that degenerated leiomyomas may show similar changes. In most of our cases, the unusual appearance of the tumor at operation was incorrectly attributed to degeneration of a leiomyoma.

Leiomyosarcoma has been classified grossly into two types: (1) sarcoma arising in pre-existent leiomyoma, the so-called "sarcomatous degeneration of a fibroid"; (2) primary sarcoma arising in the myometrium. In some cases, there may be great difficulty in deciding this point. Primary sarcomas may be nodular and may occur in association with leiomyomas. In an advanced case, it may be impossible to reconstruct the origin. As might be expected, the incidence of the two types shows considerable variation when we compare the series reported. Novak and Anderson<sup>1</sup> cite 39 to 50 cases, or 78 per cent, as developing in myomas. Kimbrough<sup>2</sup> gives 26 to 43 cases, or 60 per cent, as secondary. Wheelock and Warren<sup>3</sup> classify 32 of 35 cases, or 91 per cent, as arising in leiomyomas. In our series, 14 of 16 cases, or 88 per cent, were classified grossly as arising in leiomyomas, a figure which agrees more nearly with that of Wheelock and Warren than with those of the other authors cited.

**Histologic Criteria.**—The literature reveals a considerable difference of opinion concerning the histologic criteria for the diagnosis of leiomyosarcoma. Corseaden and Stout<sup>4</sup> take the somewhat pessimistic view that none of the histologic criteria are reliable, and insist on evidence of infiltration, metastasis or recurrence as the only valid evidence of malignancy. McFarland<sup>5</sup> similarly states that metastasis is the only proof of malignancy. Bosse and Stanton<sup>6</sup> believe that gross or microscopic evidence of invasiveness is the most reliable criterion of malignancy. Other authors, however, have found good correlation between histologic criteria and the degree of clinical malignancy. Evans,<sup>7</sup> and Novak and Anderson<sup>1</sup> classified their cases of leiomyosarcoma on the basis of mitosis counts and found that the degree of mitotic activity rather closely paralleled the clinical malignancy. Proper and Simpson<sup>8</sup> classified their series of cases into three groups according to the degree of immaturity of their cells, and found that this paralleled the degree of clinical malignancy. Recently Wheelock and Warren<sup>3</sup> analyzed their series of 35 cases, using twenty histologic criteria of malignancy. On this basis, they distinguished three grades of sarcoma. Grades 2 and 3 they considered clinically malignant, while grade 1 was considered clinically benign.

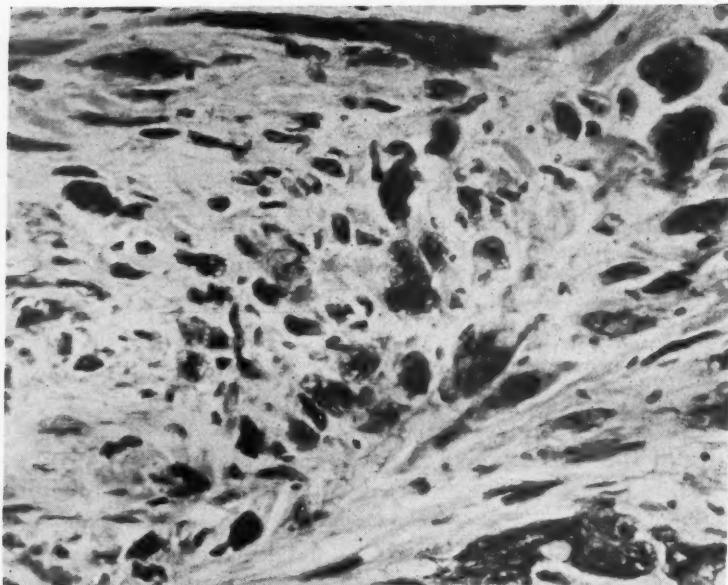


Fig. 1.—Case No. 5, unequivocal leiomyosarcoma, Grade 4, marked pleomorphism with numerous tumor giant cells is a striking feature. Hematoxylin and eosin,  $\times 370$ .

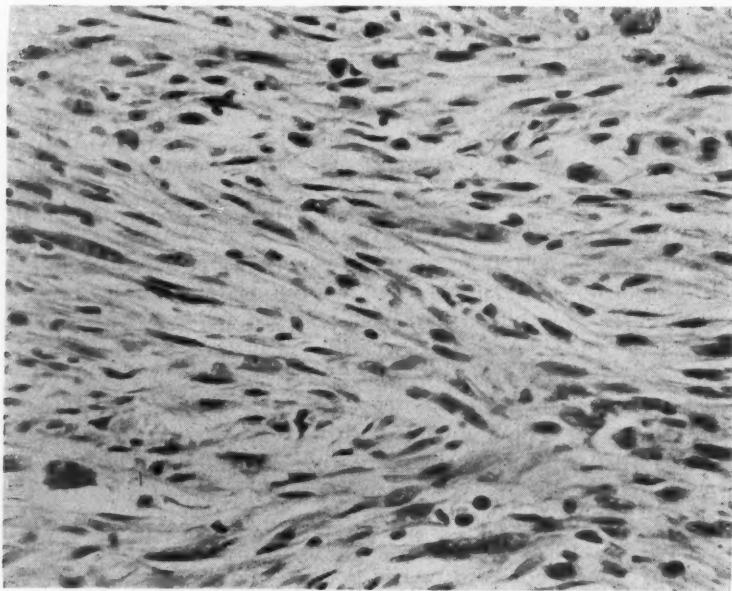


Fig. 2.—Case No. 4, unequivocal leiomyosarcoma, grade 3, characterized by moderate pleomorphism, numerous mitotic figures, and a moderate number of tumor giant cells. Hematoxylin and eosin,  $\times 370$ .

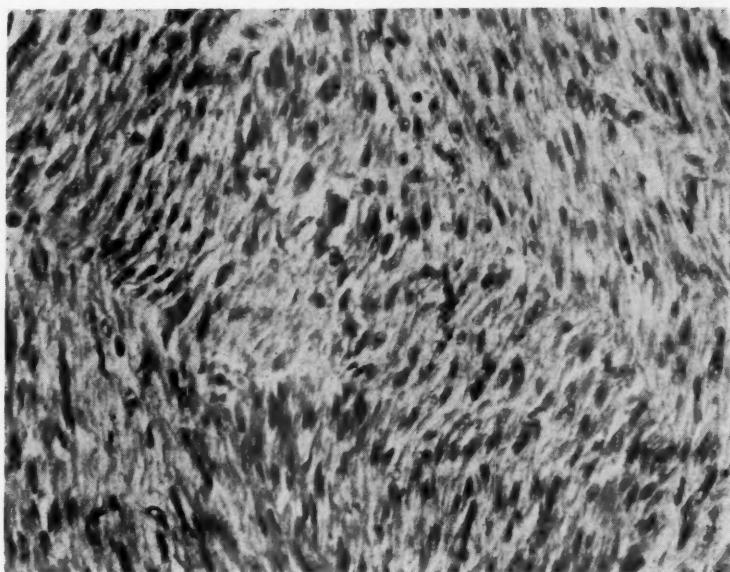


Fig. 3.—Case No. 11, low grade leiomyosarcoma, grade 1. The cells are moderately immature and occasional giant cells and mitotic figures are seen. Hematoxylin and eosin,  $\times 370$ .

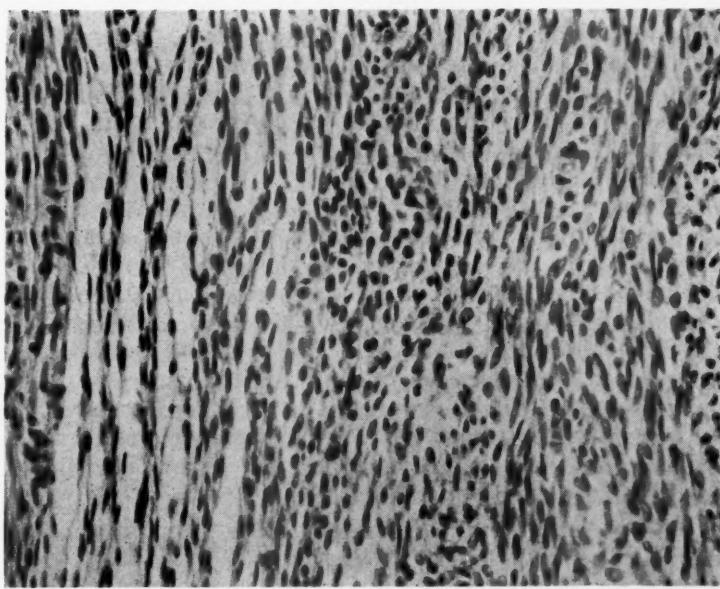


Fig. 4.—Cellular benign leiomyoma. Note maturity and uniformity of cells. Hematoxylin and eosin,  $\times 370$ .

It is apparent that the varying histologic criteria account to a considerable extent for the disagreement in statistics on the incidence of leiomyosarcoma, as well as on the survival rates. Thus, Foot<sup>9</sup> states that "leiomyosarcoma is more academically than actually malignant, and rarely metastasizes." However, Novak and Anderson<sup>1</sup> report a five-year survival rate of 30 per cent in their series of 59 cases, which included all types of uterine sarcoma. Kimbrough<sup>2</sup> cites a comparable figure of 34.3 per cent of five-year survivals in his series of 43 cases.

We have studied our cases histologically, according to the following criteria:

1. Cellularity
2. Anaplasia (degree of cell immaturity)
3. Pleomorphism (variation in cells)
4. Relative frequency of tumor giant cells
5. Relative frequency of mitotic figures
6. Invasiveness

Histologic invasiveness, while a valuable criterion of malignancy when present, was of little use in our series, since it was present in only 2 of 16 cases.

Each case was rated on each of these criteria on a scale of 1 plus to 4 plus. By averaging these values, a histologic grade was assigned to the tumor. The rating was done on representative sections and as objectively as possible, although it is recognized that there is an inescapable subjective factor in any such grading.

On further analysis of the four grades of tumors, it became apparent that they fell readily into two main groups. The first of these, comprising grades 3 and 4, showed to a considerable degree the classical histologic features of malignancy, and for this group we propose the term unequivocal sarcoma. The diagnosis of sarcoma in this group would probably cause little disagreement among pathologists, except for those who insist on invasiveness, recurrence, or metastasis as evidence of malignancy. It is interesting that originally one of these, Case No. 4, was diagnosed as "probable sarcomatous degeneration of a leiomyoma." Another, Case No. 10, was diagnosed as "marked degeneration of a fibroid." On re-examination, the few better preserved areas showed unequivocal sarcoma, although most of the tumor was too necrotic for satisfactory diagnosis.

The second group, comprising grades 1 and 2, showed less striking evidence of malignancy and would doubtless cause considerable disagreement among pathologists as to diagnosis and prognosis. On the basis of this series, we feel that tumors in this group cannot be dismissed as clinically benign, but may show a tendency to local invasion and recurrence, although perhaps not to metastasis. For this group we propose the term low grade leiomyosarcoma.

A third group of cellular, but benign leiomyomas, we have purposely excluded from this study. This comprised a fairly numerous group (approximately 11 per cent of leiomyomas) in which the tumor was unusually cellular, and some of which showed as many as 10 mitotic figures per high power field. However, the cells were uniform and mature.

*Clinical Data.*—An analysis of the age range, symptoms, and signs is given in Table III.

The patients in this series were all white; 9 were nulliparous, 6 multiparous, and 1 unknown. The average age was 47.2 years, with a range of 34 to 73 years. The greatest incidence, 10 cases, was found in the 40 to 50 year period. The major symptoms are noted above. Only six patients were aware of an enlarging pelvic or abdominal mass, although in all 16 pelvic examination revealed a readily palpable tumor. It must be remembered that

symptoms are often produced by, or are relative to, the associated leiomyomas and accurate differentiation is difficult. Five cases revealed a severe anemia, the hemoglobin range being 5.9 Gm. to 10.3 Gm.

TABLE III. CLINICAL DATA

Total No. Cases	16
30-40 years	2
40-50 years	10
50-60 years	2
60-70 years	1
70-75 years	1
<i>Symptoms and Signs</i>	
Menorrhagia	8
Metrorrhagia	4
Postmenopausal bleeding	3
Abdominal pain	3
Watery diarrhea	3
Weight loss	2
Enlarging mass	6
Severe anemia	5

Tables IV through VII give a detailed analysis of the cases, including the pertinent pathologic data, the operative procedures, and the results.

TABLE IV. 1917-1948

Total Number of Cases	16
No Follow-up	3
Inadequate Follow-up	2
Alive to date	5
Without recurrence	3
With recurrence	2
Deaths	6
Autopsies	2
Mortality Rate (known)	54.5%
Survival (known)	45.5%

In the following discussion we have considered only those cases in which the outcome is known to date. Two of our cases had follow-up examinations at nine months and one and one-half years, respectively, but both have been excluded because no further follow-up has been obtainable in many years. In Table V is noted our small group of three patients living and well to date without recurrence.

It is interesting but not conclusive that our two patients above who had subtotal hysterectomies have to date shown no pelvic recurrence. The site of origin in each case was a fundal leiomyosarcoma and each was graded as un-

TABLE V. PATIENTS ALIVE WITHOUT RECURRENCE

CASE NO.	AGE	SOURCE	GRADE OF LEIOMYOSARCOMA	OPERATION	FOLLOW-UP
2	44	Leiomyoma (Fundal)	Unequivocal	Subt. hysterectomy Lt. Sal.-oophorectomy Rep. femoral hernia	1 1/12 yrs.
3	40	Leiomyoma (Fundal)	Low-grade	Total hysterectomy Bil. sal-oophor.	1 1/6 yrs.
5	44	Uterine wall	Unequivocal	Subt. hysterectomy	3 3/4 yrs.

equivocal. The postoperative period of each is brief, one and one-twelfth and three and three-fourths years, and obviously one can draw no conclusions as yet as to recurrence or final outcome.

TABLE VI. PATIENTS ALIVE WITH RECURRENCE

CASE NO.	AGE	SOURCE	GRADE OF LEIOMYO-SARCOMA	OPERATION	RECURRENCE
6	42	Leiomyoma	Unequivocal	Total hysterectomy Bil. sal-oophor. (prior curettage)	Hemi-colectomy for sarcoma, mass terminal ileum at $4\frac{1}{2}$ yrs. Living to date $4\frac{1}{2}$ yrs.
11	48	Leiomyoma	Low-grade	Subt. hysterectomy Bil. sal-oophor. Appendectomy	Exc. 2 omental sarcoma masses at $6\frac{1}{2}$ yrs. Living to date $7\frac{2}{3}$ yrs.

In case 6 the diagnosis of leiomyosarcoma was made by curettage, and the complete operative procedure was dictated by the laboratory diagnosis. There were no omental nor small bowel adhesions at the time of hysterectomy. Recurrence at four and one-sixth years of sarcoma in the terminal ileum was diagnosed by x-ray following a four months history of asthenia, anorexia, severe anemia terminating in "bloody stools." We interpret this recurrence as a blood stream metastasis of an unequivocal sarcoma. Surgical exploration revealed no pelvic or abdominal recurrence; exhaustive x-ray studies have been negative. The patient is well at  $4\frac{1}{2}$  years, but the prognosis is very guarded due to the grade of the sarcoma (unequivocal), and the possibility of other undemonstrated metastases. Case 11 is interesting in that the initial tumor mass was a pedunculated leiomyoma, the source of the low-grade leiomyosarcoma. We were not able to substantiate the presence of omental adhesions, which we suspect may have been present. We can only say that six and five-sixth years after the initial operative procedure, two discrete omental leiomyosarcomatous masses were removed; again the pelvis and the remainder of the abdominal cavity revealed no recurrence. The patient is living and well over nine months after her recurrence and seven and two-thirds years after her initial operation.

In both the above cases the recurrent tumors were identical in structure with the primary uterine sarcomas. Furthermore, the smooth muscle origin of the recurrent sarcomas was proved by their characteristic staining reaction with Masson's stain.

Table VII shows that all deaths were cases of unequivocal sarcoma, and each case reveals evidence of spread based on autopsy, operative, or x-ray findings. Case 1 revealed the entire uterus to be a mass of leiomyosarcoma. Direct and lymphatic extension had occurred to the bladder, right tube and ovary, left adrenal, retroperitoneal lymph nodes, gastrocolic omentum, peripelvic and sacral lymph nodes; there was an associated fibrinopurulent peritonitis. Case 4 was characteristic of spread by blood stream. Autopsy revealed no local pelvic lesions or involved glands, but there were distant metastatic lesions in the lungs and right auricle. Case 9 showed a huge inoperable pelvic mass, the size of a five months' gestation, with marked bowel invasion, probably a spread by both contiguity and lymphatics, in the opinion of the operator. Fractional x-ray was given with no apparent effect. Autopsy was not obtained. Case 10 was an example of amputation of the uterus through a portion of the tumor with apparent pelvic spilling. Seven months later exploratory laparotomy revealed the pelvis filled with an inoperable tumor mass; biopsy was

TABLE VII. DEATHS

CASE NO.	AGE	SOURCE	GRADE OF LEIOMYOSARCOMA	OPERATION	SURVIVAL	AUTOPSY
1	73	Uterus (in-deter-minate)	Unequivocal	Inoperable: Biopsy of tumor	2½ mos.	Sarcoma in uterus, rt. tube, ovary, bladder, omentum, etc.
4	42	Leiomyoma (Fundal)	Unequivocal	Subtotal hysterectomy, Bil. sal.-oophor. Appendectomy	16 mos.	Metastatic sarcoma of lungs and rt. auricle
9	46	Leiomyoma	Unequivocal	Inoperable: Biopsy of tumor	3 mos. (died in hospital)	No autopsy. Inop. sarcoma invading bowel
10	46	Leiomyoma	Unequivocal (with de-gen. & ne-crosis)	Subtotal hysterectomy	9 mo. (died at home)	No autopsy. Expl. operation, Biopsy implant. on pelvic peritoneum at 7 mos.
12	34	Leiomyoma (Fundal)	Unequivocal	Subtotal hysterectomy, Lt. sal.-oophor.	2½ yrs. (died at home)	No autopsy. Pulmonary metastases by X-ray at 2 yrs.
14	51	Leiomyoma	Unequivocal	(1) Myomectomy (vaginal) with drainage (2) Subtotal hysterectomy (6 wks. after above)	6 plus weeks (died 2 d. post-op.)	No autopsy "Masses in sigmoid and omentum"

made of an implant on the pelvic peritoneum. Death at home followed in two months. Case 12 showed spread via the blood stream to the lungs, demonstrated by x-ray. Death occurred at home nine months after x-ray studies, and no autopsy was obtained. The local doctor believed "there was no pelvic or abdominal recurrence" but this opinion was unsubstantiated by reliable examination or autopsy in Case 14. Sarcoma was first diagnosed after vaginal excision of a submucous leiomyoma. Laparotomy six weeks later was apparently a heroic attempt to remove a large uterine sarcomatous mass. Great difficulty was experienced in control of bleeding, and the patient died on the second postoperative day. No autopsy was obtained.

### Discussion

We believe that leiomyosarcoma can be diagnosed with reasonable accuracy from histologic criteria. A division into two grades seems justifiable, and for these we propose the terms "unequivocal leiomyosarcoma" and "low grade leiomyosarcoma."

The gross appearance of 14 of our 16 cases differed from that of an ordinary leiomyoma. However, these could be easily confused with a degenerated leiomyoma. We would suggest that any leiomyomas which are unusually soft, friable, or of unusual color should be viewed with suspicion and incised, after removal, at the operating table. Immediate consultation with the pathologist, with frozen section examination when necessary, may establish the correct diagnosis and permit the proper complete surgical procedure to be performed. In the absence of such consultation, the gynecologist should con-

sider the advisability of performing a more radical procedure when he encounters grossly atypical leiomyomas or those with a history of rapid growth, particularly in the age group over 40 years.

It is suggested that at operation the omentum, if adherent to leiomyomas, should be widely excised. In one of our cases recurrence in the omentum occurred six and five-sixth years after hysterectomy for a low grade sarcoma.

In one case of our series, local and pelvic implantations occurred within seven months, following incision through a supposed "degenerated leiomyoma" in the course of a subtotal hysterectomy. This illustrates the danger of a too-limited surgical approach, creating a pelvic spill of the tumor. To date, this is the only early case in our series showing cervical or pelvic recurrence. As a further point in surgical approach, it is suggested that traction on the round ligaments or adnexa is safer than tenaculum traction on a leiomyomatous uterus, to avoid tearing a friable leiomyosarcoma with possible resultant spill of tumor particles.

In our series, the most common type of sarcoma (14 of 16 cases) was that arising in a leiomyoma. In this group, we have observed metastasis by blood stream, and by direct extension. In one case demonstrating lymphatic metastasis, the exact site of origin in the uterus was indeterminate.

Our series suggests that leiomyosarcoma arising in the fundus rarely recurs in a retained cervical stump, providing the site of excision is well below the involved area. In spite of this we feel that total hysterectomy with bilateral salpingo-oophorectomy, when the operative status of the patient warrants it, is the procedure of choice.

### Summary

1. Sixteen cases of leiomyosarcoma of the uterus occurring in a thirty-year period at the Methodist Hospital, Brooklyn, New York, are reviewed.
2. Histologic criteria are suggested for classifying these under two types, unequivocal leiomyosarcoma and low grade leiomyosarcoma.
3. The unequivocal leiomyosarcomas tend to metastasize widely, as well as to implant locally.
4. The low grade leiomyosarcomas may recur in contiguous structures after relatively long periods.
5. Of 16 cases, 11 had adequate follow-up. Of these, six, or 54.5 per cent, died of metastases within two and three-fourths years. Three cases are living and well, without recurrence. Two cases have had further operative procedures for recurrences, but to date are living and well with no recurrences demonstrable.
6. Autopsy findings in two cases of leiomyosarcoma are reported.

We are indebted to the members of the Surgical and Gynecological Staffs of the Methodist Hospital for permission to include their private cases in this series.

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### Discussion

DR. J. EDWARD HALL.—I take exception to some of the slides that have been presented here, just as I did when I first saw them.

This is a relatively rare disease, as both speakers mentioned. It has an incidence of 1.4 per cent in the experience of most workers. Kelly and Cullen, in 1,400 fibromyomas, reported an incidence of 1.2 per cent; Maisson, in 4,000 fibromyomas, had an incidence of 1 per cent. The incidence percentage in our own institution, of 1,238 cases, was less than 1 per cent.

I think that it is important to understand percentages when they are given. Dr. Howe, when he started his presentation, stated that sarcomas of the uterus represented 5 per cent of the malignancies of that organ. It must be understood that this is uterine sarcoma and not fibromyoma. Consequently, the figures for both of these conditions are misunderstood. In the Johns Hopkins Hospital, 4 per cent of all uterine malignancies consisted of sarcoma of the uterus.

I wonder whether actually some of the patients who have lived a long time had recurrences of the original tumor, or represented multiplicity of tumor formation. In the case of a patient who after 20 years presents a lesion histologically similar in character to one previously removed, it can very easily be assumed to be from the lesion that was removed originally. At our institution, we recently had a patient who was operated on for multiple myomas of the uterus. Just before closure of the abdomen, as is the custom, the entire peritoneal cavity was explored. A tumor of the small intestine was found which, on histologic examination, proved to be a neurogenic sarcoma. If this lesion had not been found until many years after the pelvic operation, it might have been assumed to have been related to the pelvic tumor. In these instances, two slides, one from the original operation and one from the present operation, are required. A comparison of these slides will show whether the patient has a sarcoma of the uterus at the time of the original surgical procedure and whether the present tumor was a metastasis in the intestine, a frequent situation in such cases.

Involvement of the ileocecal valve in sarcoma of the uterus is a rare condition. Sarcoma of the uterus metastasizes by direct extension through the lymphatics and blood stream, therefore involvement of the liver and lungs is fairly common, but involvement of the ileocecum is unusual.

With respect to the material removed by curettage, again I would question whether it was a myoma of the uterus or diffuse sarcoma of the uterus, possibly from the endometrial tissue itself, from the myometrium, or from the blood vessels of the uterine musculature.

It must be remembered that, embryologically, all uterine tissue arises from the mesoderm; therefore, you may have sarcoma from the myomatous element and also from the epithelial component.

Another point with respect to the anatomy of the myoma is that there is no such thing as a definite capsule of a myoma. Because there is loose areolar tissue separating the myomatous tissue from the surrounding normal uterine musculature, we are apt to think that we separate the myoma from the diffuse normal musculature of the uterus by stripping away the capsule. Histologically, there is no such thing as a capsule as, for example, in the case of a cyst. Therefore, it is easy to understand that if you are dealing with a sarcoma in dissection, especially in a myomectomy, malignant cells may be diffused. That

brings up a very important point, namely, we are apt to be lulled into a false sense of security due to the rarity of the disease, and therefore perform only a supracervical hysterectomy.

I agree with Dr. Davis 100 per cent. Every uterus and every ovarian cyst removed supravaginally should be opened and examined by a competent pathologist at the time of operation to determine the character so that all indicated surgery may be carried out at one operation rather than making it necessary for the patient to return for further surgery.

Dr. FRANK R. SMITH.—Anyone who has listened to this discussion, based on a series of ten cases, will, naturally, ask himself the question: "What possible value can it have?" If you think of the rarity of the condition, you must realize that it takes a long time to collect ten cases of what Dr. Howe chooses to call "unequivocal" sarcoma of the uterus.

I think it was in 1940 that I reported a series of sarcomas of the uterus from Memorial Hospital, covering the period from the time records were made there up to that year. I was able to collect quite a group of so-called sarcomas of the uterus. However, there were only 24 of the so-called "unequivocal" sarcomas. I wish I had known of that term at the time, because to me the term "unequivocal" meant that Doctors James Ewing, Sr., and Fred Stewart agreed that they were real sarcomas. Many patients are sent to us at Memorial Hospital who have had tumors removed elsewhere; slides are sent along with them and these have been classified as sarcomas, whereas, in reality, they are simply cellular myomas.

Another question that occurs to me is the old terminology of malignant degeneration of a fibroid. I have been looking back for such evidence and was successful in finding only one such case; a patient, mentioned by Dr. Frank Foote, of multiple fibroids of the uterus. In that instance the major part of one tumor was composed of simply cellular myoma, and the center looked like a real "unequivocal" sarcoma. That patient, however, did quite well with a simple subtotal hysterectomy.

Of the 24 cases collected, none of the patients lived five years. One patient lived four and one-half years following a supracervical hysterectomy. In cases in which supracervical hysterectomy has been done, however, this not being our usual custom, we have found recurrences in the cervix.

Another thing, I do not think sufficient emphasis has been placed on the matter of x-ray therapy. Constantly we are beset by doctors who have removed uteri, and a diagnosis of sarcoma has been made. I know of no instance of "unequivocal" sarcoma of the uterus where the patient has really derived any benefit from x-ray therapy. X-ray irradiation does not affect leiomyosarcoma of the uterus.

I was interested in hearing Dr. Hall's statement, because we recently have had a patient on whom a hysterectomy for large multiple fibromyoma of the uterus was performed. During the course of the exploration we pulled out a mushroom-like growth which was connected at about the junction of the jejunum and ileum; it looked like a mushroom umbrella and was somewhat softer than the average fibromyoma. Under the microscope it was found to be a leiomyosarcoma with a small base. I did not resect the gut beyond the point of closing it where I resected the growth, and am frank to admit I may not have done enough, although, as I say, the base was very small.

## **ENDOMETRIOSIS AS A CAUSE OF ILEAL OBSTRUCTION\***

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**T**HIS paper presents the first analysis of clinical data of a series of cases in which ileal obstruction was caused by endometriosis. The subject is of particular significance because the obstructive involvement of the distal part of the ileum by this highly invasive nonmalignant tissue often has been confused clinically with appendicitis accompanied by ileus, with malignant lesions causing obstruction of the intestine, and with intestinal obstruction caused by the adhesions of pelvic inflammatory disease. The importance of endometriosis as a cause of ileal obstruction has not been sufficiently stressed. The clinical picture of this condition, as revealed by a detailed analysis of the clinical data of sixteen cases, will be presented, as will also (1) certain facts highly pertinent to the differential diagnosis, (2) pathologic lesions and (3) surgical treatment.

The term "endometriosis" indicates the existence of endometrial tissue in any extrauterine location.

### **Pathogenesis**

Counseller classified the theories of the development of endometriosis into three main groups as follows: (1) embryonic pathogenesis, (2) metaplastic pathogenesis, and (3) migratory pathogenesis.

The embryonic theory presupposes a maladjustment on an anatomic basis. The metaplastic theory, in which it is stated that the peritoneum can undergo a change to endometrial tissue, is based on the fact that all genital epithelium and the peritoneum have a common origin from the celomic mesothelium.

The migratory theory assumes that endometriosis has its origin in the uterine mucosa and reaches its extrauterine position by contiguity or invasion, by implantation, and by lymphatic or venous metastasis.

The single theory which best explains all types of endometriosis is that of lymphatic and venous metastasis,<sup>13, 22</sup> but Sampson's implantation theory plus Harbitz' idea of extraperitonealization seem best to explain endometrioma of the ileum.<sup>7, 10, 11, 18</sup>

### **Historical Review of Cases**

Mouat, in 1926, reported the first case in which stricture of the ileum was caused by misplaced endometrial tissue on record in the *Quarterly Cumulative Index Medicus*. Starr, in 1929, published a case of endometrioma of the terminal part of the ileum, the appendix, and the cecum, with acute partial intestinal obstruction. The preoperative diagnosis had been acute appendicitis with perforation and partial intestinal obstruction. Of particular interest was the fact that the uterus and adnexa were normal. An unusual aspect of

\*Abridgment of a part of a thesis submitted by Dr. McGuff to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

the subject was presented when Gale reported an endometrioma of the ileum which had produced intestinal obstruction of sufficient degree to cause impaction of a fish bone and resultant perforation. The bowel exhibited fibrous puckering, with peritoneal adhesions and thickening of the intestinal wall at one point. On microscopic examination, the wall of the bowel was seen to be invaded by endometrial-like tissue.

In 1934, Goodwin<sup>8</sup> presented a case in which chronic intermittent partial intestinal obstruction of the ileum had been caused by endometriosis. He believed that fibromyoma and uterine retrodisplacement were frequently associated with endometriosis, and that they were possible etiologic factors. Behrendt and Neumeyer<sup>2</sup> in 1936 reported a case in which chronic partial ileal obstruction had been caused by endometriosis in a single woman, thirty-nine years of age.

Glenn and Thornton<sup>6</sup> in 1940 published two cases of endometriosis of the ileum with chronic partial intestinal obstruction. They remarked that a review of the English literature for the previous twenty years (1920 to 1940) had revealed only four cases of endometrial implants in the small intestine, with some degree of obstruction present. Grigsby<sup>9</sup> in 1941 presented two cases in which ileal obstruction had been caused by endometriosis. He noted that the most prominent gross characteristic of endometriosis was the presence of "disintegrating purplish-black blood cysts" on the intestine. Milnor,<sup>14</sup> also in 1941, reported a case of ileal obstruction caused by an endometrioma.

Morrin,<sup>15</sup> in 1942, described a case of complete ileal obstruction caused by endometriosis, and Wood, Diebert, and Kain,<sup>23</sup> in 1946, reported a similar case.

#### Nature of Present Study

To the time of this report, forty-eight cases are on record in the files of the Mayo Clinic in which the diagnosis of "endometriosis of the bowel" had been made by a pathologist. In three of these cases, pathologic material had been removed during treatment of the clinical symptoms of ileal obstruction caused by endometriosis; an analytic clinicopathologic study of these three cases was made. Thirteen cases of ileal obstruction caused by endometriosis, as reported in the literature, were reviewed. From this, a combined series of sixteen cases of ileal obstruction was assembled.

#### General Considerations

All patients were white women. The average age of the women was 39.2 years. The oldest was fifty years old and the youngest was thirty-one years old. Ten of the women were in the fourth decade, five were in the fifth decade and only one was in the sixth decade. Eight of the women were married; two were widows; six were single.

Four women complained of absolute sterility, one complained of relative sterility, and two complained of secondary sterility. Among the eight women who had been married and two of the single women, there had been nine pregnancies, with the birth of seven children. In the group of women who had been pregnant, the average period since the last pregnancy was fifteen years. Two of the group previously had undergone pelvic surgical operations.

The average duration of the symptoms of endometriosis was 1.6 years. Five of the patients had complained of acquired dysmenorrhea. The menstrual cycle of eight of the patients was fairly regular, but five patients complained of irregular menstruation. Menorrhagia was a complaint of three women, and metrorrhagia was a complaint of one.

### Signs and Symptoms

The average time since the onset of the first symptoms of obstruction of the bowel was 2.3 years. Only two of the patients had lost weight. One had lost 15 pounds (6.8 kg.) and the other, 27 pounds (12.2 kg.). Rectal pain and the passing of grossly bloody stools were not complained of by any patient. Six of the patients complained of menstrual constipation, seven complained of intermenstrual constipation, and eight complained of either menstrual or intermenstrual constipation. Diarrhea was a complaint of only one patient.

Consideration of the more direct symptoms of obstruction of the lower part of the small intestine revealed that abdominal pain was the complaint of all sixteen patients. Abdominal distention was the complaint of thirteen patients, and vomiting was a complaint of twelve of the group. Obstipation occurred in five patients. Abdominal tenderness was present in seven patients, and an abdominal mass was palpated in three.

The site of intestinal obstruction in all sixteen of the patients was the distal part of the ileum. Four patients had complete intestinal obstruction, seven had partial intestinal obstruction, and five had chronic intermittent intestinal obstruction.

### Diagnosis

A barium enema was administered and roentgenograms of the colon and terminal part of the ileum were made in three cases, and were reported as producing positive results in two, in that the point of obstruction was localized. A plain roentgenogram of the abdomen and a gastro-intestinal roentgenogram were made in two cases. Both demonstrated obstruction of the lower part of the small intestine.

A preoperative diagnosis of endometriosis as the cause of the obstruction was made in three of the sixteen cases. A diagnosis of appendicitis with ileus was made in five cases, of carcinoma of the ileum with obstruction in one case, of carcinoid of the ileum with obstruction in another, and of obstruction of the bowel caused by adhesions from pelvic inflammatory disease in one case. No specific cause of the obstruction was ascertained in the other cases.

### Treatment

Ileal resection was uniformly the procedure of choice when endometriosis had caused ileal obstruction. Ileal resection alone was done for seven patients. Enterostomy plus ileal resection were done for one patient. An initial Witzel type of ileostomy and subsequent right hemicolectomy and ileotransverse colostomy were carried out in one patient. Ileal resection plus ileocecostomy and removal of the remaining tube and ovary were done for one patient. Ileal resection plus panhysterectomy were performed in one case. The short-circuiting operation of ileotransverse colostomy was done for one patient, and panhysterectomy alone was done in one case. In one case, the adhesions of endometriosis were separated to relieve the obstruction.

### Results

The condition of all but one of these patients had been followed by examination or by letter for one month to twenty-one years. An excellent result with complete relief of symptoms was obtained for ten patients, a good result with more than fair relief of the symptoms was obtained in three cases, a fair result was secured in one case, and a poor result was reported for two patients (from the literature series) who represented operative

mortalities. These two deaths had occurred before the advent of chemotherapeutic agents, antibiotic agents or anticoagulant preparations. One of the deaths resulted from postoperative peritonitis and the other from pulmonary embolism.

### Report of Three Cases

CASE 1.—A single white woman, forty-three years old, complained of lower abdominal cramping pain, abdominal distention, and loud, rumbling sounds in the bowel of two months' duration. She did not have nausea or vomiting. The aforementioned symptoms had been episodic, with increasing frequency. The patient stated that when the cramps became very severe, they suddenly seemed to break through the "stoppage" in the bowel and diarrhea occurred. Blood had not appeared in the stool. The patient had lost 27 pounds (12.2 kg.) in two months.

Physical examination revealed a markedly emaciated, weak, lethargic, white woman who lay with her knees flexed. The abdomen was moderately distended. Peristaltic waves were visible. Abdominal tenderness was absent.

A roentgenogram of the colon was reported as disclosing obstruction of the small intestine. Dilatation of the bowel proximal to the obstruction and a large amount of residual barium were noted.

The patient was treated medically by means of a double lumen tube; 500 c.c. of blood were transfused three times for hypoproteinemia and secondary anemia, and other supportive therapy was carried out in order to get her into the best possible condition for operation, if relief of the obstruction did not develop. The obstruction persisted and became complete one week after admission of the patient.

The patient's abdomen was explored. It was believed that ileocecal obstruction caused by a carcinoid was present. Twenty-eight days after performance of the enterostomy a second operation was done. The distal part of the ileum was found to be dilated to about twice normal size, and was edematous. There was a small mass in the region of the ileocecal juncture, the exact nature of which could not be determined. The right half of the colon, along with the distal foot of ileum, was resected, and side-to-side ileocolostomy was performed. No abnormalities were found in the pelvis and there was no evidence of endometriosis.

The patient made an uneventful recovery. She was released from the hospital on the fourteenth postoperative day. One week later she was dismissed with complete relief of the symptoms of intestinal origin. She weighed 90 pounds (40.8 kg.)—a gain of 15 pounds (6.8 kg.) since her admission.

*Pathologic Data.*—The specimen consisted of 22 cm. of the terminal part of the ileum, 16 cm. of the cecum (Figs. 1 and 2) and ascending colon, and the appendix. The point of obstruction was 5 cm. proximal to the ileocecal valve. The obstructive process consisted of an extensive blanched area of firm, stenosing endometriosis of the ileum. At the point of obstruction, the ileal mucosa was not involved, but was markedly puckered in a rosette pattern. The ileum proximal to the point of obstruction was markedly dilated to two and a half times normal size, and the wall of the ileum was markedly hypertrophied. Examination of the point of obstruction indicated that the obstruction was complete.

On microscopic examination, the inner portion of the muscularis propria and the submucosa of the ileum were seen to contain diffusely dispersed endometrial glands and stroma in the proliferative phase, and were slightly cystic. A van Gieson stain showed marked fibrosis around one area of endometrial glands and stroma.

*Comment on Case.*—This case showed how closely a portion of endometriosis of the ileum may mimic a carcinoid with intestinal obstruction in both clinical history and gross appearance.

CASE 2.—A white woman, thirty-three years old, married for nine years but never pregnant, complained of sudden, sharp, severe episodic attacks of pain in the lower and middle parts of the abdomen. She had had such extreme abdominal tenderness at other



Fig. 1.—Distal portion of the ileum and cecum removed in Case 1. An area of endometriosis had caused obstruction 5 cm. proximal to the ileocecal valve. The dilated ileum is above.

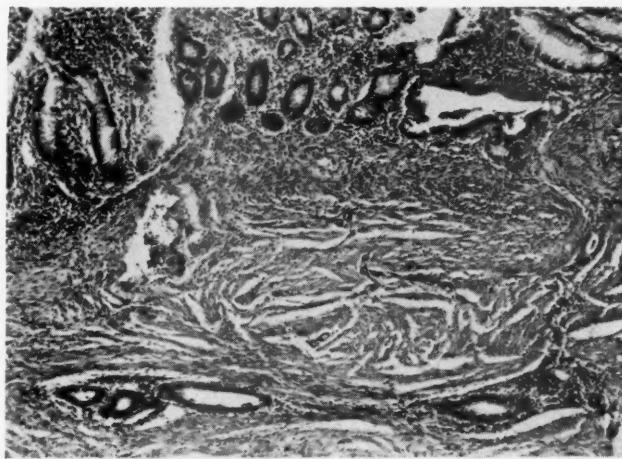


Fig. 2.—Section of the ileum removed in Case 1. Note endometrial glands and stroma in the submucosa and in one area just adjacent to the mucosa (hematoxylin and eosin  $\times 65$ .)

times that she could not walk. The pain had been worse in the few months prior to her admission. She had always been constipated. Acquired dysmenorrhea had become so severe that she would go to bed for the first day of each of her irregular menstrual periods.

On abdominal examination, tenderness in the right lower abdominal quadrant and some rigidity were found. Pelvic examination revealed an irregular, tender mass in the adnexa uteri on the right.

Abdominal exploration was performed; in the lower part of the ileum were found three small contracted and scarred areas. The middle area was the largest. It was producing partial obstruction of the terminal part of the ileum. About 6 inches (15 cm.) of the ileum, including these three areas, were removed, and an end-to-end anastomosis was made. The pathologist reported the condition as multiple endometriomas of the ileum, with partial ileal obstruction.

The patient made an uneventful recovery. She was seen twenty-one years later, at which time relief of symptoms referable to the bowel were complete.

*Pathologic Data.*—The specimen consisted of 15 cm. of ileum with three endometriomas, each about 6 cm. apart. The ileum proximal to the middle endometrioma was dilated to two and a half times normal size. The mucosa at the site of the endometrioma was puckered, not ulcerated, and was freely movable. The endometriomas were hard; their serosal surfaces had a dimpled and puckered, grayish black, speckled appearance.

Microscopic examination disclosed endometrial glands and stroma in the late differentiative phase in the external longitudinal muscular layer near the serosal side. The van Gieson stain demonstrated moderately increased fibrosis around the islands of endometrial glands and stroma.

CASE 3.—A single white woman, thirty-one years of age, who seven years before had been pregnant, the pregnancy ending in an abortion, complained of intermittent pain in the right lower abdominal quadrant which occurred one week before, during and after menses. The pain had been progressively increasing in severity for nine years. The pain increased in intensity as the period came on, and recently had begun to appear ten days before the onset of menstruation, to continue throughout the period. Recently she had had three attacks of severe pain in the right lower abdominal quadrant. In two of the attacks, maximal intensity of pain was reached immediately after the period. The pain was not related to urination or defecation. For the month prior to the patient's admission, the pain had been situated across the lower part of the abdomen and had been persistent. Heat had afforded no relief.

The patient's menses usually occurred from three to six weeks apart; a scanty flow lasted for six days. Six months previously she had had mild metrorrhagia for six weeks.

Previous surgical procedures were an appendectomy done nine years previously, and three years previously, a left radical mastectomy and right simple mastectomy for bilateral intraductal papillary carcinoma.

On abdominal examination, an unusual, ovoid, flat tumor was palpated in the region of the cecum. This tumor was movable and tender.

Abdominal exploration was performed; right salpingo-oophorectomy and resection of the terminal portion of the ileum, with ileocecostomy and end-to-side anastomosis, were done.

The postoperative diagnosis was endometriosis of the right ovary and terminal part of the ileum, with partial intestinal obstruction.

The patient made an uneventful recovery. Her condition was followed for one and one-half years, at the end of which she was free of symptoms of obstruction but was experiencing marked menometrorrhagia which apparently was due to the progression of the endometriosis.

*Pathologic Data.*—The specimen consisted of 15 cm. of ileum; 9 cm. from the proximal end there was an area of firm, infiltrating endometriosis, 3 by 2 cm. The intestine proximal to the point of obstruction was dilated to twice normal size, and was moderately

hypertrophied. The mucosa over the site of endometriosis was normal and freely movable. The serosal surface of the area of endometriosis was irregular, puckered, roughened, and speckled grayish black.

Microscopic examination of the section of ileum revealed endometrial glands and stroma in the late differentiative phase diffusely spread through the outer portion of the longitudinal muscular layer, but none were seen in the submucosa. A van Gieson stain demonstrated moderate fibrosis around the endometrial glands and stroma in the outer muscular layer.

### Pathologic Considerations

Endometriosis is the only condition of frequent occurrence in women which represents the nonmalignant invasion of other tissues by normal tissue of the same host.<sup>12</sup> Endometriosis, to persist, must have the cyclic hormonal stimulation of the ovaries; in the absence of such stimulation, endometriosis undergoes retrogression. Endometriosis invades the intestinal wall from the serosal side and grows inwardly into the muscularis propria and the submucosa. Rarely has the mucosa of the small intestine been invaded grossly. The intestinal mucosa was intact over the endometriomas in all of the cases studied. In many cases it was adherent or puckered, but it was never ulcerated.

The ileum is not so much obstructed by the pushing-in process of the endometrioma as it is by the effects of a small endometrioma accompanied by superficial adhesions, caused by endometriosis, which kink the intestine.

The tissues studied for this paper were removed surgically from three patients at the clinic. They consisted of two segments of the distal part of the ileum, and one specimen removed by right hemicolectomy. In these three cases in which ileal obstruction occurred and the pathologic material was available for direct study, the cause of obstruction was a combination of (1) an endometrioma impinging into the intestinal lumen, and (2) more superficial areas of endometrial adhesions causing a kinking of the intestine.

Associated pelvic pathologic lesions were present in eight of the patients. Uterine fibroids were found in two of the patients, chocolate cysts of one ovary or both ovaries were present in two patients, and simple ovarian cysts were present in two patients. In two of the patients, pelvic pathologic lesions had been removed at a previous operation.

Histopathologically, the endometrioma of the intestine and the areas of endometriosis consisted of either invasion of the serosa, muscularis propria, and submucosa or any combination of these, by endometrial glands and stroma. The muscularis propria more consistently seemed to contain diffusely dispersed endometrial glands and stroma than did either the serosa or the submucosa. In the ileum, it seemed that the submucosa was only lightly invaded, and the endometrial glands and stroma were dispersed more in the outer muscular layer and in the serosa. Although the endometriomas were not exactly typical of the superficial or diffuse type of endometriosis, they were less deep in situation than are the usual endometriomas of the sigmoid.

**Diagnosis.**—The first analysis of a series of sixteen cases of ileal obstruction caused by endometriosis has revealed certain important clinical data highly pertinent to the diagnosis of this condition. Comparison of clinical data from this series of cases of ileal obstruction with clinical data in a previously reported series of cases of intestinal obstruction in general caused by endometriosis indicated that ileal obstruction more often occurs in a younger group of women in their upper thirties, who either have no grossly detectable pelvic endometriosis or have much less extensive pelvic endometriosis.

In the group who had ileal obstruction, the fertility rate was higher; there were fewer associated pelvic lesions, and fewer previous pelvic surgical procedures had been performed. Also, in the group with ileal obstruction, constipation was less frequent; only one patient complained of diarrhea and no patient complained of rectal pain or bloody stools. Vomiting was of much more frequent occurrence than obstipation. Gross blood in the stool usually is not a symptom of endometriosis of the bowel. It was *not* a symptom of ileal involvement in sixteen cases.

When the ileum is obstructed by endometriosis, the prominent symptoms and signs are those of obstruction of the lower part of the small intestine, and, if the correct preoperative diagnosis is to be made, the symptoms of endometriosis generally must be searched for by means of a carefully taken history<sup>17</sup> and thorough abdominal and pelvic examinations. The general symptoms of endometriosis may or may not be present in these patients, but when they are present, the symptoms usually occur to a lesser degree. Most important points in the diagnosis of endometriosis causing ileal obstruction are: (1) sterility of ten to fifteen years' duration, (2) the presence of acquired and increasing dysmenorrhea, (3) menstrual periodicity of the symptoms of endometriosis and moderately progressive ileal obstruction, and (4) the presence of uterine fibroids or ovarian cysts and/or tender nodules in the cul-de-sac of Douglas or along the uterosacral ligaments. The "threshold of suspicion" of the physician should be aroused by the presence of any two of the aforementioned points.<sup>4</sup>

*Differential Diagnosis.*—Obstruction of the distal part of the ileum by endometriosis often has been thought clinically to be appendicitis accompanied by ileus. As a rule, however, the symptoms of endometriosis are elicited if a thorough history is taken. Definite symptoms of progressive obstruction of the lower part of the small intestine are superimposed upon the periodic menstrual symptoms of increasing acquired dysmenorrhea, abdominal pain, constipation, and so forth. The symptoms of low ileal obstruction are colicky, cramping pain in the lower part of the abdomen or about the umbilicus (usually greater on the right side), abdominal distention, constipation or diarrhea, and fairly early nausea and vomiting. Diarrhea, if present, generally is reflex in origin; if the obstruction persists, the constipation becomes obstipation. The ileal obstruction at first may be moderate in degree, but it progresses rapidly with each menstrual period, to usually acute complete or partial obstruction or to chronic intermittent intestinal obstruction of high or low grade. Ileal obstruction if persistent brings about great physiologic changes,<sup>1, 21</sup> such as dehydration, loss of chlorides and resultant alkalosis, and loss of plasma.

In five cases (one in the current series and four in the series from the literature), the preoperative diagnosis was appendicitis with ileus. None of the patients concerned had had rectal pain, and only six of the sixteen in the whole series had been constipated. Fewer proportionately (five of sixteen) complained of acquired dysmenorrhea than in a previous general series in which endometriosis also had obstructed the lower bowel; hence, it is easily seen that, in the group of ileal obstruction caused by endometriosis the symptoms of endometriosis are not so striking or prominent as were those in the general series.

The differential diagnosis between ileal obstruction caused by endometriosis and appendicitis<sup>20</sup> with ileus may be difficult. However, when a history is carefully taken, the menstrual periodicity of some of the symptoms of endometriosis and of some of the symptoms of a previous episode of "subileus" or mild intestinal obstruction, such as abdominal pain, distention, and nausea

or vomiting, usually can be elicited. This is the most important single point in the differential diagnosis between ileal obstruction caused by endometriosis and appendicitis with signs of obstruction.

About half of the patients in this group will be found to have, on pelvic examination, associated pelvic lesions such as tender, endometrial nodules in the cul-de-sac of Douglas, ovarian cysts and, occasionally, uterine fibroids. Hence, the second most important point in the differential diagnosis is the finding of associated pelvic pathologic processes or other signs of pelvic endometriosis.

Third in importance is the characteristically rhythmic chronicity of the manifestations of endometriosis as opposed to a single attack of appendicitis or to, usually, no more than one or two previous nonrhythmic attacks.

Laboratory work in the form of leucocyte counts and differential blood counts does not seem to aid much in the distinction, for in the series leucocyte counts of more than 10,000 per c.mm. often were noted, as were high polymorphonuclear counts. "Point tenderness" seems to be of the utmost importance in the diagnosis of acute appendicitis, as contrasted with the absence of this type of tenderness in ileal obstruction caused by endometriosis. It is easily understood, however, that, at times, the differential diagnosis between these two entities from the standpoint of an emergency clinical preoperative diagnosis might well be impossible.

**Treatment.**—Surgical treatment is indicated in ileal obstruction caused by endometriosis. The obstruction is caused more by the tough, dense adhesions of endometriosis and the resultant kinking of the intestine than by impingement of the endometrioma into the intestinal lumen. Hence, most of the time, the only way in which the obstruction in the ileum can be overcome, will be resection or a short-circuiting procedure, such as ileotransverse colostomy, which will not remove the lesion. This is true in respect to the ileum, even though it is a basic fact that the retrogression of endometriosis depends upon the absence of ovarian hormonal stimulation, and that bilateral oophorectomy usually produces a certain "relenting" of the lesion.

If there is extensive endometriosis of the pelvic viscera in an older woman, bilateral oophorectomy and hysterectomy also may be done. In a younger woman, with no or only slight pelvic involvement by endometriosis, ileal resection alone should prove sufficient. If the obstruction is complete or of high grade, with great dilatation of the proximal portion of bowel, preliminary enterostomy may be done to relieve the distention, the procedure later to be followed by ileal resection.

Decision to do or not to do bilateral oophorectomy should be based on the location and extent of the endometriosis in the pelvis, the presence and degree of associated pelvic pathologic processes, and the patient's desire for pregnancy and the probability of her becoming pregnant. It might be pointed out that when the pelvic part of the colon is chronically obstructed by endometriosis, bilateral oophorectomy usually is indicated, and that as a rule the bowel should be treated conservatively.

### Summary and Conclusions

An analytic study of the clinical data in sixteen cases of ileal obstruction caused by endometriosis has been presented. Three of these cases are from the files of the clinic and thirteen are from the medical literature.

Important points in the diagnosis of endometriosis caused by ileal obstruction are: (1) sterility of more than ten years' duration, (2) increasing acquired dysmenorrhea, (3) menstrual periodicity in the symptoms of

endometriosis and moderately progressive ileal obstruction, and (4) the presence, in half of the cases, of tender nodules in the cul-de-sac of Douglas or along the uterosacral ligaments, or of uterine fibroids or ovarian cysts.

Obstruction of the distal part of the ileum by endometriosis often has been thought clinically to be appendicitis accompanied by ileus. The symptoms of endometriosis generally can be elicited, however, if a thorough history is taken.

The clinical picture of ileal obstruction caused by endometriosis is much less characteristic than that of sigmoidal obstruction.

The treatment of choice in ileal obstruction caused by endometriosis is ileal resection, with or without preliminary ileocolostomy or enterostomy and with or without bilateral oophorectomy and/or hysterectomy, as indicated by the presence and degree of the associated pelvic pathologic processes.

The mechanism of ileal obstruction was found to be due, usually, to kinking caused by the adhesions of endometriosis and, to a lesser degree, to the impingement of the endometrioma into the intestinal lumen. Endometriomas of the ileum were more superficial in location than those of the pelvic part of the colon.

Microscopically, reactive fibrosis around the endometrial glands and stroma was characteristic. Endometrial glands and stroma were found in all layers of the intestinal wall except the mucosa. They were more prominent, however, in the muscularis propria and the serosa.

Histopathologic examination of frozen sections of tissue and pathologic confirmation of endometriosis as the cause of ileal obstruction are imperative in every case, because a malignant process can be excluded only by this procedure.

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## ACUTE HYDRAMNIOS

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**A**CUTE hydramnios is apparently very rare. Bequain<sup>1</sup> determined that it occurs once in 12,000 deliveries. O'Driscoll<sup>2</sup> reviewed the reported cases in the literature and found only 90 which could be classified as acute. Chronic hydramnios, on the other hand, is much more common. Tweedy<sup>3</sup> has reported an incidence of one in 262 deliveries, and Ryder<sup>4</sup> one in 177 deliveries. In the present study there were four cases of acute hydramnios in 49,793 deliveries at the New York Hospital, an incidence of one in 12,448, a figure closely approximating that of Bequain.

The material for this study was gathered from a review of charts of 115 cases in which a tentative diagnosis of hydramnios was made by any one observer in the antepartum clinic or in the hospital. If subsequent examination of any individual patient in the clinic or hospital did not again suggest hydramnios, the case was discarded from this series. On that basis 49 cases were excluded from the present presentation. Of the remaining 66 cases, it was felt that four corresponded to the type referred to in the literature as acute hydramnios. Because of the extreme rarity of this condition, the four cases are presented in detail.

CASE 1.—(60858.) The patient, a para 0, gravida i, was first seen in the antepartum clinic in the twentieth week of gestation. The past history was not remarkable, and the antepartum course had been uneventful. Physical examination revealed the fundus to be 20 cm. above the symphysis, the weight was 54 Kg., and the pelvis was normal. The Wassermann reaction was negative; and there was no albumin in the urine. The hemoglobin was 74 per cent. The blood pressure was 130/75. At the time of her second visit, in the twenty-fourth week of gestation, there was no essential change in her condition. In the twenty-eighth week, however, she complained of progressive dyspnea, backache, and acceleration of the abdominal enlargement of one week's duration. There was no history of trauma. The abdomen was extremely tense and firm, and there was a two-plus edema of the lower extremities. The weight was 60 Kg., and the height of the fundus was measured at 27 cm. above the symphysis. A diagnosis of acute hydramnios was made, and she was immediately admitted to the hospital. Twelve hours later the membranes ruptured spontaneously. The amount of amniotic fluid could not be measured. Labor began thirty minutes later, and after seven hours she delivered a 2,400 Gm. female stillborn infant. The blood loss was 200 c.c. The postpartum course was uneventful and afebrile. Three years later and again six years later she had full-term spontaneous deliveries of living children without hydramnios.

CASE 2.—(54330.) The patient, a para i, gravida ii, was 24 years of age and had delivered a normal 8-pound infant four years previously. She registered in the antepartum clinic in the twenty-seventh week of gestation. The Wassermann reaction was negative; the urine was negative for albumin, and the hemoglobin 72 per cent of normal. The weight was 67 Kg. and the fundus 25 cm. above the symphysis. The pelvis was normal. On the next clinic visit, ten days later, she complained of excessive abdominal enlargement, pain across the

entire upper abdomen, edema of the lower extremities, and headaches. A diagnosis of acute hydramnios was made, and she was admitted to the hospital. Two days later an x-ray of the abdomen was suggestive of a hydrocephalic infant. The membranes were ruptured artificially and 4,500 c.c. of amniotic fluid were measured. Labor did not ensue, and three medical inductions of labor using castor oil, quinine, and intranasal pituitrin were given. Five days after the rupture of the membranes she delivered a 2,360 Gm. stillborn hydrocephalic infant with cyclops. The duration of labor was twelve hours, and the blood loss was 150 c.c. The postpartum course was uneventful and afebrile. There is no record of subsequent pregnancies.

CASE 3.—(79774.) The patient, para ii, gravida iv, was 32 years of age, and had delivered two full-term normal infants, had one abortion at three months, and had delivered a deadborn infant in the seventh month. The latter had occurred two years previously, and the antepartum course had been complicated by hydramnios. She registered in the antepartum clinic in the twenty-second week of gestation. At that time she complained of marked acceleration of the abdominal enlargement of about three weeks' duration. This had embarrassed her respirations and had caused nausea. Physical examination revealed the skin of the abdomen to be smooth and glistening. The uterus filled the abdomen from the symphysis to the xiphoid, and the abdominal circumference at the umbilicus measured 109 cm. The Wassermann reaction was negative, and there was no albumin in the urine.

She was immediately admitted to the hospital and treated by limitation of fluid intake and oral administration of magnesium sulfate. Under this regime she lost 4.4 kg. and became much more comfortable. She was discharged from the hospital after thirty-five days. Ten days after discharge, in the twenty-seventh week of gestation, labor began spontaneously, and after eighteen hours the membranes ruptured spontaneously with passage of a copious amount of amniotic fluid. After twenty-two hours of labor she delivered a 950 Gm. macerated fetus which presented by breech. There were no congenital abnormalities. The fetal heart had not been heard at any time during the pregnancy. The postpartum course was normal except for slow involution of the uterus.

Two years later she delivered a 3,140 Gm. living infant after an antepartum course complicated by moderate hydramnios.

CASE 4.—(194221.) The patient, para 0, gravida i, was 25 years of age, and registered in the ninth week of gestation. Physical examination at that time was entirely normal, and the Wassermann reaction was negative. In the fourteenth week of gestation she suffered a severe fall, and after that time noticed increased abdominal enlargement. She did not again present herself for examination until the eighteenth week of gestation. Examination at that time revealed the abdomen to be enlarged to the size of a term pregnancy. The circumference of the abdomen at the level of the umbilicus was 90 cm. The height of the fundus was 31.5 cm. above the symphysis. The next day labor began spontaneously and after four hours and ten minutes she delivered twins weighing 270 and 300 Gm., both of which made feeble attempts at respiration. There were no congenital abnormalities. The amniotic sac of the first infant contained only a small amount of fluid, whereas 2,500 c.c. were measured from the second sac, and it was estimated that another 1,000 c.c. escaped. Examination of the membranes revealed that the infants were uniovular twins. The attachment of the second umbilical cord was definitely velamentous. The blood loss was 40 c.c. The postpartum course was uneventful and afebrile. The patient delivered normal full-term infants five and seven years later without hydramnios.

It should be noted that three of the above cases delivered in the twenty-eighth week of gestation and one delivered in the eighteenth week. In all the cases the diagnosis was made prior to the onset of labor and one patient was treated in the hospital for thirty-five days. The treatment was expectant with attempts at dehydration in all except the second case in which the membranes were ruptured artificially after an x-ray diagnosis of hydrocephaly had been made. There were no infant survivals. One case occurred after

trauma and the infants were uniovular twins. The amounts of amniotic fluid was actually measured in two cases. In one it was 4,500 c.c. in the twenty-eighth week, and in the other it was 3,500 c.c. in the eighteenth week of gestation.

### Chronic Hydramnios

There is another larger group of cases in which the accumulation of an excessive amount of amniotic fluid is more gradual. The patient is able to compensate for the reduced thoracic capacity, and does not necessarily suffer acute respiratory distress. The pregnancy usually continues to term, and the fetal mortality is much lower. This type has been called moderate or chronic hydramnios.

There were 62 cases in the present series which corresponded to this type, an incidence of one in 794. Three of these occurred in twin pregnancies. There were 14 cases, or 23 per cent, in nulliparous patients, and 48, or 77 per cent, in multiparous patients. It would be impossible to present all of these cases in detail, but a brief analysis has been made and is presented in Tables I and II.

TABLE I. AVERAGE MATERNAL STATISTICS

Age of patient	30.5 years
Weight gain during pregnancy	10.2 Kg.
Height of fundus prior to delivery	32.3 cm.
Week diagnosis was made	36th week
Week delivered	38th week
Duration of labor in primiparas	26 hours
Duration of labor in multiparas	11 hours
Amount of amniotic fluid recorded in 17 cases	4,300 c.c.
Blood loss at delivery	209 c.c.
Weight of infant delivered in single pregnancies	3,165 Gm.
Weight of infant delivered in twin pregnancies	2,390 Gm.

TABLE II. CONCURRENT COMPLICATIONS

COMPLICATIONS	NO. OF CASES	INCIDENCE
<i>Obstetric Complications</i>		
Eclampsia	1	1.6%
Severe pre-eclampsia	4	6.4%
Mild pre-eclampsia	6	9.6%
Puerperal infection	3	4.8%
	14	22.4%
<i>Intercurrent Diseases</i>		
Syphilis	3	4.8%
Rheumatic heart disease	3	4.8%
Hypertensive disease	2	3.2%
Diabetes	2	3.2%
Pyelonephritis	1	1.6%
Acute nephritis	1	1.6%
Myoma uteri	1	1.6%
Kyphoscoliotic dwarfism	1	1.6%
	14	22.4%
Total		44.8%

In the group of chronic hydramnios there was one maternal death from acute pyelonephritis due to *B. coli*. The case occurred prior to the advent of sulfonamide therapy. A brief summary is presented below.

CASE 5.—(52021) A 35-year-old, gravida viii, para iv, Negro woman with a negative Wassermann reaction was first seen in the antepartum clinic in the seventeenth week of gestation. She gave a history of having had excessive abdominal enlargement with previous pregnancies. On admission to the hospital in the thirty-ninth week she gave a history of having had lower abdominal pain, fever, burning on urination, and right flank pain for two weeks. Physical examination revealed the fundus extending almost to the xiphoid and there was some respiratory distress. Three days after the development of false labor, the membranes were ruptured artificially. Two thousand five hundred cubic centimeters of amniotic fluid were measured with an estimated 1500 c.c. remaining in the uterus. Labor was then stimulated by enema, castor oil, and intranasal pituitrin. After twenty-one hours of labor she delivered a 4,220 Gm. deadborn infant. The fetal heart tones had not been heard during the eight hours preceding delivery. The blood loss was 400 centimeters. One hour before delivery the temperature had risen to 38.6° C. but returned to normal immediately after delivery. On the third postpartum day it was again elevated. The patient was cystoscoped with drainage of cloudy urine from the right kidney pelvis. *B. Coli* was cultured from this urine. The patient then improved for several days, but later suddenly developed signs of generalized peritonitis and expired on the fifteenth postpartum day. At autopsy acute inflammation and abscess formation were found in the right kidney. There was also a moderate amount of inflammation in the left kidney.

### Fetal Mortality

The prognosis for the infant in hydramnios has always been recognized as being very poor. Krahula<sup>5</sup> reported a series of 207 cases of hydramnios from the Bonn Clinic and stated that a total of 28 children left the hospital alive and healthy. Floris,<sup>6</sup> in a study at the Kermauner Clinic in Vienna, reported 236 cases from which 183 infants were born viable and were discharged from the hospital in good condition. Ryder<sup>4</sup> reported that of the 141 infants delivered in his 113 cases, there were 76 survivals.

Of the 65 infants (three cases of twins) in the present review of chronic hydramnios, 31, or 48 per cent, were born alive and left the hospital in good condition. Of the 34 infants which did not survive there were 17 deadborn, 10 stillborn, and seven neonatal deaths. In Table III the causes of the fetal deaths are given.

TABLE III. FETAL DEATHS

CAUSES	NO. OF CASES	INCIDENCE
Congenital anomalies	19	29%
Anencephaly	12	
Achondroplasia	2	
Spina bifida and teratoma of the buttocks	1	
Hydrocephaly	3	
Congenital heart defect	1	
Erythroblastosis	7	11%
Other causes	8	12%
Total	34	52%

The majority of the cases of erythroblastosis were of the hydrops type, thus accounting for the fetal deaths in that group. Javert,<sup>7</sup> in a study of erythroblastosis, noted that the diagnosis of hydramnios was often made clinically because of excessive uterine enlargement. He found that the average weight of the fetus plus the placenta in 16 cases of erythroblastosis of the hydrops type was 4,674 grams. The average period of gestation in this group was thirty-six weeks. This illustrates the fact that the diagnosis of hydramnios can frequently be made erroneously in such cases.

In the congenital anomaly group the fetal mortality cannot be improved, but early diagnosis through the use of the x-ray is of great value in the management of such cases. An x-ray diagnosis was made prior to delivery in nine of the 12 cases of anencephaly. Beck<sup>8</sup> has emphasized the value of this procedure and states that the patient can be spared considerable suffering if the diagnosis is made early. Payne and Bland<sup>9</sup> reviewed the literature in 1942 and found only 31 cases where x-ray diagnosis had been made prior to delivery.

The eight cases listed under "Other Causes" (Table III) are presented in detail below because it was only in those cases that there was any possibility of securing a healthy living infant.

CASE 6.—(C.P.) The patient was a multipara. She sustained a fall in the thirty-second week of pregnancy. At the next clinic visit two days later a statement was made that there was probably excessive amniotic fluid. The fetal heart was not heard, and several days later she no longer felt fetal movements. In the thirty-sixth week of gestation 5,000 c.c. of amniotic fluid were measured when the membranes were ruptured artificially. At that time there was found a marginal placenta previa and a Braxton Hicks version was performed. After two hours and forty-eight minutes a macerated infant weighing 2,540 Gm. was delivered.

CASE 7.—(M.S.) This case was presented in detail as the one of maternal death above. The fetal heart was last heard eight hours prior to delivery.

CASE 8.—(A.H.) The patient was a multipara. The membranes ruptured spontaneously soon after the onset of labor, with the passage of a large unmeasured amount of amniotic fluid. The fetal heart rate varied between 40 and 90 immediately afterward. Four hours later the fetal heart could not be heard and the umbilical cord was found in the vagina. The infant weighed 5,420 Gm. and was deadborn.

CASE 9.—(A.J.) The patient was a multipara. The diagnosis of hydramnios was made fourteen days before delivery. After twelve hours of labor the membranes were ruptured artificially, but the amount of amniotic fluid was not recorded. A slightly macerated infant was delivered three hours later. The fetal heart had not been heard during labor.

CASE 10.—(O.R.) The patient was a multipara. She was known to have a myomatous uterus. During labor the myoma obstructed the passage of the fetus and it had to be delivered by version and breech extraction. There was no maceration. The amount of amniotic fluid was estimated to be 5,000 cubic centimeters. Autopsy of the infant revealed intracranial hemorrhage.

CASE 11.—(S.S.) The patient was a primipara. She fell and sustained rather severe trauma to the abdomen in the thirty-fifth week of gestation. She came to the hospital immediately and hydramnios was noted. One month later she was again admitted to the hospital and given a medical induction. Soon afterward the membranes ruptured spontaneously, and after fourteen hours of labor a 3,660 Gm. infant presenting by face was delivered. The child died within twenty-four hours, and the autopsy revealed subarachnoid and subdural hemorrhages.

CASE 12.—(R.K.) The patient was a multipara. Hydramnios was diagnosed one month prior to delivery. The membranes ruptured spontaneously prior to the onset of labor. The total duration of labor was forty-six hours. The patient developed intrapartum infection with the loss of fetal heart tones two hours prior to delivery. Since the pelvis was adequate, it was felt that dystocia was the result of a constriction ring. The infant was deadborn and weighed 4,440 grams.

CASE 13.—(M.F.) The patient was a multipara. In the thirty-fourth week of gestation the patient began to bleed quite profusely. She was admitted to the hospital where a diagnosis

of hydramnios and partial placenta previa was made. The membranes were ruptured artificially but the amount of amniotic fluid was recorded only as "excessive." Labor began eight hours later, and after twenty-three hours a living 2,700 Gm. infant was delivered spontaneously. It had attacks of cyanosis and died of bronchopneumonia five weeks later.

In one case the death of the infant was probably not the result of hydramnios, i.e., Case 10 where it was the result of birth trauma associated with a myomatous uterus. In Case 6 it is difficult to determine the cause of fetal death. It apparently occurred concurrently with the development of hydramnios after trauma. In Cases 11, 12, and 13 it was the result of complications following malpresentation, desultory labor, and placenta previa, respectively. All of these have been mentioned in the literature as complications of hydramnios. In Cases 7, 8, and 9 fetal death occurred at various intervals after the artificial or spontaneous rupture of the membranes, and could have been due to mechanical obstruction of the umbilical cord. This was more definite in Case 8 than in the other two. Six infant deaths were then indirectly attributable to hydramnios.

#### Treatment

The conservative approach to the treatment of hydramnios has always been more acceptable, such treatment consisting of rest in bed, limitation of fluids and salt, and either medical induction of labor or rupture of the membranes from below if the maternal distress becomes too great. Since 1919, however, other forms of therapy have been reported in the literature. Chief among these is the aspiration of the amniotic fluid through the abdominal wall. Schatz,<sup>10</sup> in 1882, first recommended but did not actually perform the procedure. Although it is reported to have been performed previously, Henkel<sup>11</sup> reported the first case in 1919, and Wormser<sup>14</sup> reported soon afterward. At first the procedure met with considerable criticism in Europe and was said by Seitz<sup>12</sup> to be useless and not without danger. Subsequently, however, it has come into more common usage and has been adopted in England and America. Rivett<sup>13</sup> has reported the greatest number of cases, and in a recent report stated that he has used the procedure in about 50 cases. He found that "Live babies resulted in over 25 per cent of cases which required some treatment before viability of the fetus." He reported one case in which labor was delayed nine weeks after removal of nine pints of fluid and resulted in the delivery of a normal child.

The advocates of the abdominal aspiration method of treatment maintain it to be superior to the vaginal approach inasmuch as the danger of infection is thereby reduced. Furthermore, the release of the amniotic fluid abdominally can be so well controlled that labor does not ensue. They admit that there are many theoretical dangers, but contend that there has never been a serious accident.

A tabulation of the results with respect to the infant in some of the reported cases of abdominal aspiration is given in Table IV. Of the thirty-nine reported cases there were twelve twin deliveries, making the total number of infants fifty-one. Results with respect to the infant were not given for sixteen of the fifty-one infants. Of the thirty-five infants in which the result was given there were eighteen infants which did not survive. This gives an infantile mortality rate of fifty-one per cent. Several of the deaths, however, occurred in infants with congenital anomalies. In seven cases the dead infant was one of twins, the other of which survived.

Another method of treatment consisting of injection of saccharin into the amniotic fluid was recommended by de Snoo.<sup>23</sup> He reported twenty cases

TABLE IV. RESULTS FOLLOWING ASPIRATION METHOD OF TREATMENT

	TOTAL INFANTS	SINGLE PREG.	TWIN PREG.	ALIVE	DEAD	RESULT NOT STATED
Henkel (1919)	1	1	-	-	-	1
Wormser (1920)	2	2	-	1	-	1
Goldschmidt (1924)	3	1	1	-	3	-
Rivett (1933)	15	5	5	9	6	-
Parvey (1933)	2	-	1	-	2	-
Mayer (1937)	15	9	3	2	1	12
Grant (1938)	1	1	-	1	-	-
Mukherjee (1939)	8	8	-	3	3	2
Feltstrom (1943)	2	-	1	-	2	-
Erskine (1944)	2	-	1	1	1	-
Total	51	27	12	17	18	16

in which the pregnancies were carried to full term. Abrams and Abrams<sup>24</sup> have recommended the administration of ammonium chloride in rather large doses, and report two cases successfully treated by that method.

In the present series the therapy of the chronic cases was conservative with limitation of fluids and salt. There were no cases in which abdominal aspiration of the amniotic sac was performed. The membranes were ruptured artificially before the onset of labor and before term in four cases. In each instance it was done because of maternal complications such as cardiac disease, acute nephritis, and severe pre-eclampsia. In six cases the membranes were ruptured artificially at term before the onset of labor. In the majority of instances, the diagnosis of fetal monstrosity had been made previously. Labor was induced by medical means in three cases.

Cesarean section was performed in two cases. One was performed because of kyphoscoliosis with contracted pelvis, and the other because of severe pre-eclampsia. Delivery was by midforceps in two cases, low forceps in five cases, breech extraction in seven cases, version and breech extraction in two cases, and spontaneous delivery in 44 cases.

#### Summary and Conclusions

1. All cases of hydramnios in the first 49,793 deliveries at the New York Hospital are reviewed in a statistical analysis, and several are presented in detail.
2. There were four cases of acute hydramnios, or an incidence of one in 12,500 deliveries, and 62 cases of chronic hydramnios, or an incidence of one in 794 deliveries. The results of this study indicate that the incidence of acute hydramnios is approximately that reported in the literature; the incidence of chronic hydramnios, however, is far less than usually reported.
3. There was one case of maternal death from pyelonephritis in the group of cases of chronic hydramnios.
4. The fetal mortality was 100 per cent in the four cases of acute hydramnios. The uncorrected fetal mortality in the chronic cases was 52 per cent. Of the 34 infants which did not survive, 19 had congenital abnormalities, seven had erythroblastosis and eight were otherwise normal.
5. X-ray diagnosis of anencephaly was made in nine cases prior to delivery. Since it has been shown in this study and in the literature that there is a correlation between congenital anomalies and hydramnios, it is felt that x-ray

examination of the abdomen should be performed in all cases in which hydramnios is diagnosed.

6. Abdominal aspiration of the amniotic sac was not performed in any of the cases.

7. The fetal mortality in 39 cases treated by abdominal aspiration of the amniotic fluid and presented in the literature is 51 per cent. This corresponds closely to the fetal mortality in the chronic cases in this study.

8. Abdominal aspiration of the amniotic fluid perhaps should be reserved for those cases of acute hydramnios in which maternal distress is so great that intervention before viability of the fetus is indicated. In our reported series this condition arose once in 12,448 deliveries. We believe that abdominal aspiration should never be performed in cases of chronic hydramnios.

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## CERVICAL OBTURATION WITH INFLATABLE CANNULA IN UTEROTUBAL INSUFFLATION AND HYSTEROSALPINGOGRAPHY

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**C**ERVICAL obturation is of major importance in the technical procedure of uterotubal insufflation and hysterosalpingography. Regurgitation of CO<sub>2</sub> gas or oil leads to unreliable estimation of the pressure employed, and not infrequently to wrong interpretation as to tubal patency. Obturation is usually secured by pressing a rubber or metal acorn against the cervical os. This is easily accomplished in the presence of a round and well-shaped external orifice. However, if the external os is irregular in contour as in lacerations and eversions, excessive pressure must be exerted by the acorn in order to prevent leakage of the contrast medium or of CO<sub>2</sub> gas as the case may be. To prevent regurgitation the cervix must be grasped firmly with a tenaculum forceps exerting counter pressure. In this maneuver, the uterus is either pushed upward or drawn down. To keep the balance by equal push and pull is sometimes difficult. The anatomic change in position may occasionally be sufficient to simulate closure of the tubes by causing artificial kinks at the uterotubal juncture or by artificially stretching adhesions which do not otherwise obstruct the tubal lumen when the normal position of the uterus is undisturbed. The cannula devised by Colvin with screw tips of various sizes, later modified by Hudgins, affords tight obturation but involves a certain amount of trauma which theoretically may predispose to embolization.

After many years experience with hysterosalpingography and uterotubal insufflation the prerequisites of an ideal uterine cannula appear to be the following:

1. Its application should be painless and unaccompanied by trauma.
2. It must provide airtight obturation of the cervical canal.
3. It should maintain the normal anatomical position of the uterus.

The cannula presented in this paper has been devised with these desiderata in view. It is based on a rather old device, namely, the use of an inflatable rubber bulb in order to change the diameter of a rigid instrument. Nitze, the inventor of the cystoscope, made use of this principle for a ureteral catheter. In 1883, a United States patent was granted to Henry E. Finney for an instrument based on the same principle for "the treatment of the male urethra." About twelve years ago, one of us (I.C.R.) constructed a cannula similar in principle to the one about to be described. Dr. R. B. Stout had the same idea, except that he placed the rubber balloon within the uterine cavity.<sup>1</sup> Decker,<sup>2</sup> in a recent publication, also recommends inserting the rubber balloon surrounding the cannula tip into the uterine cavity. This principle has been employed by one of us in studying the differential between uterine and tubal contractions during uterotubal insufflation.<sup>3</sup>

The present cannula (Fig. 1) has developed out of a simple model which we have used since 1946 in 175 cases for cervical obturation. The cannula has the length and diameter of an ordinary uterine sound. It consists of two metal channels, one of which is very narrow and ends about 2 cm. behind the tip of the instrument. Its opening is covered by a thin, elastic rubber tube, 2 to 3 cm. long, which is tied at each end to the shaft of the instrument by surgical silk.\*

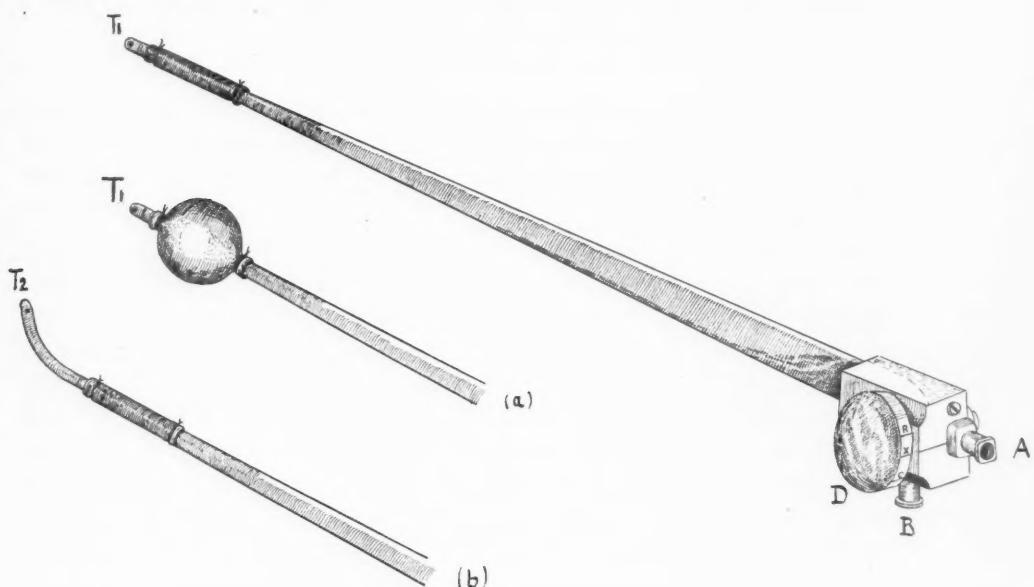


Fig. 1.—Cannula assembled ready for use with revolving disc, hubs for syringe and manometer connections and inflatable tip (letter B below letter C not visible). (a). Rubber tubing distended. (b). Extension tip for insertion into uterine cavity.

The instrument can be inserted easily into any cervical canal which admits a uterine sound. In most cases it is not necessary to grasp the cervix with a tenaculum forceps. The latter can be removed as soon as the rubber-covered tip has been inserted inside the cervical canal. In certain cases, e.g., stenosis of the internal os, it may be desirable to insert the cannula with its tip in the uterine cavity. For such purpose the short tip (T) (Fig. 1) may be replaced by a longer one (T<sub>1</sub>) (Fig. 1). Preliminary dilatation, when desirable, should not be done just before the injection of contrast media or before insufflation. So far it has been possible in our cases to introduce the cannula in cervical stenosis after the latter was passed by a uterine sound.

The cannula is inserted with the revolving disc D in the position that presents the engraved letter B (bulb on the disc) (Fig. 1) opposite a fixed indicator. Through hub A, which fits the Luer syringe, 1 to 3 c.c. of water or air are injected and thus the rubber tube at the end of the instrument becomes distended (Fig. 1a). With a little experience one can soon feel whether the bulb is sufficiently expanded. If one is interested in checking the pressure in the inflated balloon, he need only turn the disc to C, remove the syringe, and attach a manometer to hub A. On turning the disc back to B, the pressure within the rubber balloon will be promptly indicated on the manometer. It is to be noted

\*The cannula presented here is made and distributed by United Surgical Supply Co., 160 E. 56 Street, New York, N. Y.

that if less than 1 c.c. of air or water is used to inflate the balloon, the pressure readings in the balloon may not be accurate. Now the disc is turned to the position marked by the letter *C* (closed) and the instrument is ready for the procedure.

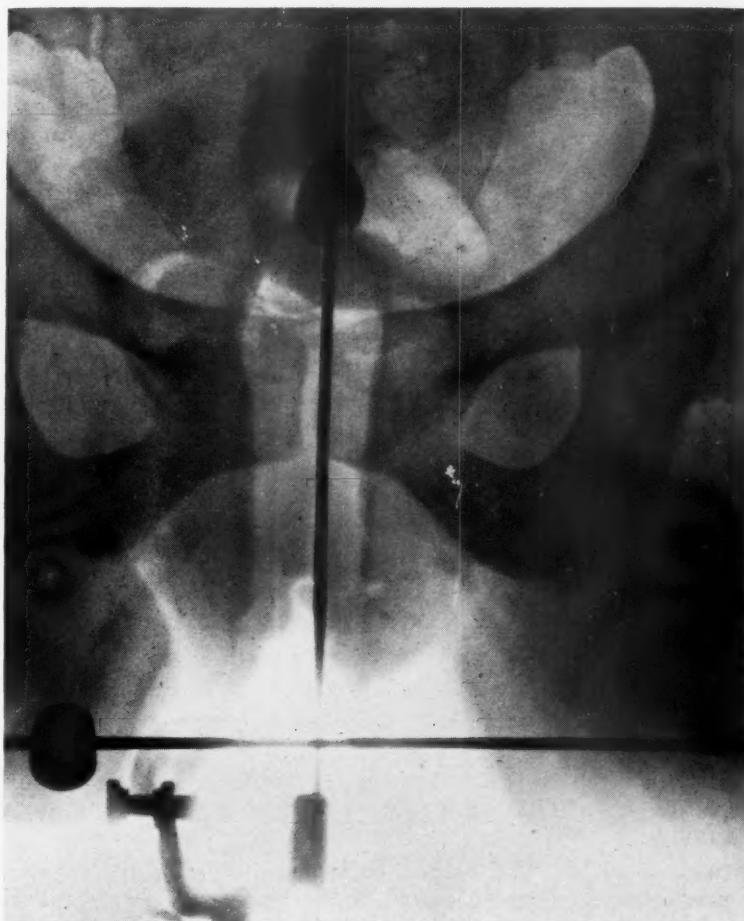


Fig. 2.—Inflatable cannula filled with diodrast obturating the cervical canal. Note that it is pyriform or acorn in shape as compared to the oval-shaped inflated cannula outside of the body.

The disc is now turned to the position *X* (= x-ray) thus connecting hub *A* directly with the tip of the instrument inside the cervical canal, or to tip *T<sub>2</sub>* in the uterine cavity. A Luer syringe containing the contrast medium is connected to hub *A* and the medium is injected into the uterus and the x-ray exposure follows. For fractional injection of contrast medium, the disc is turned to position *C* after the first fraction is introduced. Hands and syringe may now be removed because the expanded bulb retains the cannula *in situ*.\* By turning the disc back to position *X* the second fractional injection can be made, and if need be, a third or fourth.

When the kymograph is employed it is connected to hub *A* and the disc is turned to position *X*. The insufflation test can be carried out with a 20 c.c.

\*A special clamp adaptable to any vaginal speculum has been devised to keep the cannula in the horizontal position.

Luer syringe attached to hub *A*. The disc is turned to position *R* (= Rubin test) which enables us to measure the exerted pressure by connecting the manometer to hub *B*. In the simplified test, 20 c.c. of carbon dioxide injected by a syringe is sufficient because of the complete closure of the cervix without any leakage. A sudden fall of manometric pressure is indicative of tubal patency. If shoulder pains result they are minimal.\*

By inflating the rubber bulb with an aqueous contrast medium (e.g. diodrast) one can easily demonstrate the relation of the bulb to the cervical canal (Fig. 2). In order to note the distensibility of the intracervical balloon and any changes that the cervical walls might exert upon it, another cannula with the balloon filled with an equal amount of diodrast was exposed at the same time on the same x-ray film. The shape of the balloon inside the cervix may be compared to the external balloon in Fig. 2. In Fig. 3, water has replaced the diodrast and is therefore invisible, while the uterine cavity is seen filled with contrast medium. Incidentally, the cervical balloon reveals a configuration which does not conform to what one notes in conventional drawings of the cervical canal because of distention by the rubber balloon. The cervical canal appears, from our study, to yield readily to a greater degree of dilatation than has hitherto been realized.†

Owing to rigid walls, some cervices were found to resist balloon distention with 2 to 3 c.c. of water. Nevertheless, good obturation could be obtained with less filling. If the rubber part of the instrument is not inserted deep enough into the cervical canal the balloon may bulge through the external os. However, this does not prevent airtight closure. Should the rubber bulb be pushed out entirely from the cervix it may be reinserted and kept in place by grasping the anterior lip of the cervix with a tenaculum forceps. In several cases the cervix was found transformed into a shallow cone. Airtight closure could be obtained in these cases by advancing the expanded rubber bulb into the cone while the cervix was held in place by a tenaculum forceps.

The present cannula has the advantage over the ordinary cannula with an acorn tip in that it brings a larger area of the endocervix in contact with the acorn. Hence, the pressure required to obturate the cervix is less. As this pressure is not only directed upward, but upon all sides, dislocation of the cervix does not as a rule result.

The pressure within the rubber balloon automatically predetermines the maximum pressure which is intended to be used for the insufflation test or salpingography. If, for example in the bulb is 250 mm. Hg and the pressure used during insufflation or salpingography is higher, no matter how little this may be, there is prompt escape of the gas, or oil from the cervix. The same physical law operates here as in measuring blood pressure. If the blood pressure exceeds the pressure in the armcuff, the pulse wave immediately returns. The balloon in the present cannula thus forms a desirable safety valve which automatically prevents an undue increase of pressure inside the uterus.

This feature of the instrument is of importance for salpingography. Usually a contrast medium is used which has a certain viscosity. Pressure determinations when lipiodol or other viscous fluid is used are not accurate because of the considerable friction inside the small lumen of the cannula where a rapid decrease of pressure takes place with each progressive centimeter of the lumen. When the contrast medium enters the uterine cavity the

\*The senior author does not recommend or employ the use of the syringe for injecting CO<sub>2</sub> into the uterus for testing tubal patency, preferring insufflation by means of the automatic siphon meter with kymograph. The present cannula is admirably adapted for this apparatus.

†This point of elasticity of the cervix under various conditions will be the basis of a future publication.

pressure inevitably falls. If tubal obstruction is encountered there is a gradual increase of pressure inside the uterus until it equals that which is exerted by the syringe. Before this point is reached a high pressure may be exerted through the syringe which is not usually appreciated by the operator unless he uses a manometer. The rubber balloon affords safety because when the pressure exceeds that within the bulb, the oil escapes at once through the external cervical os.



Fig. 3.—Inflatable cannula filled with water (therefore invisible by x-ray) obturating the cervical canal. The contrast medium (rayopaque) demonstrates the uterine cavity. The rubber balloon distended by diodrast is seen below outside of the body for purpose of comparison.

The instrument can be sterilized by boiling. The rubber bulb can stand boiling many times; its cost, however, is so small that it may readily be replaced for each test. We have found it practical to fill the bulb before inserting the cannula in order to note whether it is watertight. However, should the rubber break it is immediately appreciated by the drop in resistance. The water escapes through the external os and does no harm. It is particularly to be noted that the operation of the cannula is exceedingly simple, and after some little experience, requires a minimum of time.

### Conclusions

The importance of cervical obturation in the procedure of uterotubal insufflation and hysterosalpingography has been emphasized. Desiderata of the ideal uterine cannula are:

1. Painless application unaccompanied by trauma.
2. Airtight closure of the cervical canal.
3. Maintenance of the normal anatomical position of the uterus.

A new cannula with inflatable balloon for cervical obturation has been described.

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## THE DIAGNOSIS OF GENITAL MALIGNANCY BY VAGINAL SMEARS\*

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HERE has been a very noticeable increase in life expectancy within recent years. Inflammatory diseases are no longer foremost in the cause of death. Undoubtedly this is the result of improved technics and better facilities for diagnosis and treatment.

Cancer, on the other hand, now rates second among the causes of death in the United States. Concurrent with this advance in death rate from cancer there has been a remarkable increase in public sentiment toward the disease. Scientific interest and civilian pressure both are activating stimuli to the study of early diagnosis and early treatment of malignancy. Physicians as well as laymen must remember that cancer is curable, but to be cured, it must be diagnosed early.

In 1944, there were 171,171 deaths due to cancer in the United States. Of these, 89,005 occurred in women. Genital cancer was responsible for 22,140 deaths. Because of this preponderance of female genital malignancy, our interest has centered on the vaginal smear as an aid in the early diagnosis of the disease.

### Methods

Smears are obtained on all new patients who come to the obstetric and gynecologic clinics, and are requested on all return patients over 30 years of age. Secretions from clinically suspicious genital lesions are obtained for study. It is preferred that a patient does not take a douche on the morning of the expected visit to the clinic. This is not always possible on the first visit, but for subsequent visits it becomes routine.

Two types of smears are made; vaginal and cervical. We believe that neither of the two should be omitted. Frequently, a third type, endocervical or endometrial, is employed according to Papanicolaou and Marchetti.<sup>1</sup>

The smears are obtained, stained, and classified according to the works of Papanicolaou<sup>2</sup> and Papanicolaou and Traut.<sup>3</sup> The details of these procedures as we use them have been reported previously by our group.<sup>4</sup>

### Results

So far in this study, 6,753 smears on 1,709 patients have been examined. Malignancy was diagnosed by pathology in 124 of these patients. Malignancy was diagnosed by vaginal smears in 114 of these 124 patients, an error of 8.1 per cent. Those missed may be divided into three groups consisting of: (1)

\*A part of the expenses incurred in this study was defrayed by funds from a grant to one of us (W.K.C.) by the Research Council of Duke University. The greater part of the expenses, however, was defrayed by funds from a grant to one of us (J.R.K.) by the North Carolina State Laboratory of Hygiene.

†Trainee, National Cancer Institute.

insufficient tissue or poor fixation, three patients; (2) smears obtained after roentgen therapy, three patients; (3) smears missed through not recognizing cancer cells though present, 4 patients.

False positive diagnoses were made in 34 of the remaining 1,585 patients, an error of 2.1 per cent.

TABLE I. SUMMARY OF FALSE POSITIVE SMEAR DIAGNOSES

<i>Patients who had had irradiation for carcinoma</i>	
Carcinoma clinically; negative biopsy	1
Carcinoma clinically; no biopsies	5
Carcinoma clinically; pathology of biopsy doubtful	1
No carcinoma clinically; negative biopsies	6
No carcinoma clinically; no biopsies	3
	16
<i>Other patients</i>	
Those who had negative biopsies	11
Those who have had no biopsies or follow-ups	3
Those who had suspicious biopsies; no follow-ups	4
	18
Total	34

### Reports of Patients

The following patients are presented in order that the diagnoses obtained from vaginal smears and biopsies may be compared.

CASE 1.—M. P. The patient, a Negro married woman aged 61 years, para 19-6-7, was seen first in our clinic on May 26, 1947. Her chief complaint was: "Something protruding from my birth canal for seven years." She had had an uneventful menopause eleven years prior. The history elicited four episodes of vaginal spotting during the past eighteen months; the last bleeding was ten days prior to the first visit to the clinic. There was no leucorrhea. The preliminary diagnosis was: postmenopausal bleeding, cause undetermined; chronic cervicitis; prolapsus uteri I-II; cystocele; rectocele. A biopsy made at the time of the first visit was reported as chronic cervicitis. A diagnosis of squamous celled carcinoma of the cervix, type V, was made from vaginal smears obtained at the first visit. The second biopsy obtained on June 3, 1947, was reported as chronic cervicitis. A vaginal hysterectomy, bilateral salpingo-oophorectomy, anterior and posterior colporrhaphy and perineorrhaphy were performed on July 28, 1947. Vaginal smears were diagnosed as type V on this date. The pathology, after numerous serial sections, was reported as early squamous celled carcinoma of the cervix.

CASE 2.—S. McR. The patient, a Negro widowed woman aged 55 years, para 2-1-1, was seen first in the medical clinic for headaches and dizziness on Feb. 5, 1947. She had had an uneventful menopause two years prior. Erosion of the cervix was noted on routine pelvic examination. The preliminary diagnosis was essential hypertension and chronic cervicitis. The report on a biopsy made at the first visit was chronic cervicitis. Vaginal smears were diagnosed as squamous celled carcinoma of the cervix, type IV, at this time. The patient was followed with monthly biopsies and vaginal smears until July 27, 1947, before the smear diagnosis of Feb. 5, 1947 was confirmed by pathology.

CASE 3.—E. W. The patient, a white widowed woman aged 56 years, para 3-0-2, was seen first in our clinic on Nov. 11, 1947, for intermittent postmenopausal bleeding and lower abdominal cramps for one year and five months, respectively. She had had an uneventful menopause six years prior. The pelvic examination revealed a cystocele, a rectocele, and a normal, clean, firm, closed cervix. Speculum examination revealed a clean, well-epithelialized cervix with slight bleeding from the os. Additional bleeding occurred upon sounding the

uterine canal. The preliminary diagnosis was: cystocele, rectocele, and postmenopausal bleeding, cause to be determined. The vaginal smear diagnosis was squamous celled carcinoma, type V, on the first visit. A diagnostic dilatation and curettage and endocervical biopsy were performed on Nov. 13, 1947. The pathologic report was squamous celled carcinoma. Examination of the gross specimen obtained by Wertheim radical hysterectomy and radical pelvic lymphadenectomy revealed a clean negative portio vaginalis. An endophytic neoplasm of the endocervix was found after sagittal section of the uterus and cervix. The regional lymph nodes revealed no metastases.

CASE 4.—O. T. The patient, a white married woman aged 37 years, para 6-0-6, was seen first in our clinic on April 1, 1947, with a referred diagnosis of squamous celled carcinoma of the cervix. She had delivered, spontaneously, a full-term infant three months prior. The last two months of gestation were complicated by pre-eclampsia and intermittent vaginal spotting. There was daily spotting after delivery. Ten days prior to her first visit here, the patient had a diagnostic curettage and cervical biopsy which was reported as squamous celled carcinoma of the cervix. The pathology report on a biopsy obtained on her first visit here was chronic cervicitis without evidence of malignancy. Vaginal smears obtained on April 1, and April 7, 1947, were classified as type V, squamous celled carcinoma of the cervix. The report on a biopsy made on April 8, 1947, confirmed the original diagnosis of squamous celled carcinoma of the cervix made elsewhere. The final pathologic report on the cervix and uterus obtained following radical Wertheim hysterectomy and radical pelvic lymphadenectomy was intraepithelial cervical carcinoma.

CASE 5.—M. N. The patient, a white separated woman aged 55 years, para 7-1-6, was seen first in our clinic on Sept. 15, 1947. She was referred in by her local physician with a diagnosis of a questionable carcinoma of the cervix. She had had an uneventful menopause eight years prior. There had been daily spotting associated with leucorrhea for the past year. The preliminary diagnosis was carcinoma of the cervix, stage I-II. The pathology report on a biopsy obtained on Sept. 15, 1947 was chronic cervicitis with atypicalities of the epithelium. Vaginal smears obtained at this time were classified as squamous celled carcinoma of the cervix, type V. The pathology report on a repeat biopsy obtained Sept. 23, 1947, was epidermoid carcinoma of the cervix, spinal cell type.

CASE 6.—L. S. The patient, a white married woman aged 63 years, para 5-1-4, was admitted to the hospital on July 28, 1947. Her chief complaint was "a growth on the left side of my privates." Menopause followed hysterectomy and partial oophorectomy seventeen years before. There had been a moderate yellowish, watery, vaginal discharge. She had not experienced pruritus. Left inguinal nodes measured approximately 2 by 3 centimeters. They were firm, non-tender and movable. The clinical impression was carcinoma of the vulva with metastases. The pathological report on a biopsy made on July 28, 1947 was squamous celled carcinoma of the vulva. Vaginal smears made on July 29, 1947 were diagnosed type IV, squamous celled carcinoma of the vulva.

CASE 7.—M. H. The patient, a white married woman aged 65 years, para 3-0-0, was seen first in the clinic on Aug. 18, 1947, with postmenopausal spotting of eight months' duration. She had had an uneventful menopause fifteen years before. Six months prior to her first visit here a diagnostic curettage performed elsewhere was reported negative for malignancy. The uterus was found to be small and anterior, but there was thickening in the left adnexal region. A second curettage on Sept. 29, 1947 resulted in negative pathology. The patient was readmitted to the hospital on Nov. 7, 1947 for panhysterectomy because of continued postmenopausal bleeding. Vaginal smears obtained on Nov. 8, 1947 showed adenocarcinoma, type V. Total hysterectomy and bilateral salpingo-oophorectomy were performed on Nov. 9, 1947. The pathologic diagnosis was adenocarcinoma of the left oviduct. The edge of the tumor was reported at 3 cm. distance from the uterine cavity.

CASE 8.—M. C. The patient, a Negro widowed woman aged 78 years, para 3-0-3, was admitted to the hospital on July 9, 1947, because of postmenopausal bleeding. An uneventful

menopause occurred forty years prior. Her blood pressure was 225/120. There was cardiac enlargement. Urine showed 1 plus sugar and 1 plus albumin. Preliminary clinical impression was adenocarcinoma of the endometrium, hypertensive cardiovascular disease, generalized arteriosclerosis, and diabetes mellitus. The pathologic report on tissue removed from the cervical os was acute inflammatory reaction. Vaginal smears made on July 10 and July 15, 1947, were diagnosed type III, suspicious for adenocarcinoma of the endometrium with pyometra. The patient was administered an oral estrogen, 10 mg. twice a day starting on July 15, 1947. Vaginal smears made on July 17, 1947, were diagnosed type IV, adenocarcinoma with atypical malignant cells which did not fully correspond to descriptions of the usual endometrial adenocarcinomatous cells. A total hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed on July 18, 1947. The operation was done because of continued profuse hemorrhage associated with a soft uterus the size of a four months' pregnancy. The final pathologic report was spindle celled sarcoma of the uterus.

CASE 9.—T. G. The patient, a white married woman aged 61 years, para 2-0-0, was seen first on Nov. 21, 1947, because of postmenopausal spotting for one month. A diagnostic curettage was performed elsewhere on Oct. 27, 1947. The pathologic diagnosis was adenocanthoma of the uterus. Vaginal smears made on Nov. 21, 1947, were diagnosed type II CM, without evidence of malignancy. Repeat smears made on Dec. 9, 1947 were similar; still without evidence of malignancy. A panhysterectomy and bilateral salpingo-oophorectomy were performed on Dec. 10, 1947. Smears were obtained from the endometrial surface of the surgical specimen. Grossly, the lesion appeared most suspicious of malignancy, but the smears showed only hyperplastic endometrial cells. The tissue diagnosis was adenocarcinoma of the endometrium.

CASE 10.—M. S. The patient, a Negro woman aged 23 years, para 4-0-4, was seen in the clinic because of prolonged and excessive bleeding for six weeks. The previous menstrual period was May 15, 1947. The patient's youngest child was 1 year old. There had been no tissue passed per vaginam. The uterus was 1½ times normal size, globoid and soft. Hemoglobin was 49 per cent. A chest plate was negative. Tissue obtained by curettage on June 25, 1947, was suspicious of chorionepithelioma. After complete review of the sections by all members of the Pathology Department, the diagnosis of chorionepithelioma was made. The vaginal smear on July 1, 1947, was type V, with numerous elements of pregnancy-type cells, abortal, but with definite malignant changes. A Wertheim radical hysterectomy and radical lymphadenectomy were performed on July 2, 1947. The pathology report was chorionepithelioma, without evidence of lymph node metastasis. The patient returned on Oct. 9, 1947, with hemoptysis. A chest plate showed pulmonary metastases. Vaginal smears made at this time were diagnosed type I, pregnancy.

Patient 1 came to the clinic with symptoms of prolapsus and gave a history of vaginal spotting. Cancer was diagnosed by smears at the time but was not confirmed by pathology until two months later.

Patient 2 was seen first in the medical clinic because of symptoms of hypertension. Irritation of the cervix was noted on speculum examination. Cancer was diagnosed by smears at this time, but was not confirmed by pathology until five months later.

Patients 1 and 2 illustrate clearly the possibility of detecting early malignancy by smear studies prior to biopsy. Again it must be stressed that this is not an inherent fault of the biopsy method of diagnosis. Cells are shed into the vagina, in intraepithelial carcinoma, although there may be no visual evidence of a cervical lesion. The biopsy method, therefore, is not to be blamed if the biopsy is not taken from the involved area.

Patient 3 came to the clinic with the symptom of postmenopausal bleeding. There were no cervical changes, clinically, in spite of the history. A vaginal smear diagnosis of squamous celled carcinoma was made three days prior to D and C and endocervical biopsy. One sees in this patient the potentialities of the use of smears during the climacteric. Physicians often fail to note the menstrual irregularities which may be due to neoplasm during this

physiologic epoch. The bleeding is attributed so frequently to the climacteric if a clean, negative-appearing cervix is seen. The patient may have an endophytic cancer of the cervix. This may be true also in patients with postmenopausal bleeding, but in our clinic such bleeding is always considered as resulting from a neoplasm until all diagnostic procedures are returned as negative. The patient remains under close scrutiny indefinitely even when the studies are negative.

Patients 4 and 5 had a preliminary diagnosis of cervical carcinoma when seen first in our clinic. Confirmation of the diagnosis was made on the first visit by vaginal smears. The first biopsies obtained here were reported as nonmalignant in each patient. Patient 4, following Wertheim radical hysterectomy and radical pelvic lymphadenectomy, was found to have had an intraepithelial carcinoma. This patient again demonstrates the value of the use of vaginal smears in the diagnosis of genital carcinoma in its preinvasive stage.

The smears on patient 6 show that vulvar epithelium is exfoliated into the vagina, permitting, therefore, diagnosis of vulvar malignancy by this technic.

The smears in patient 7 were strongly positive for adenocarcinoma, although two diagnostic curettages failed to establish a diagnosis of malignancy. This shows that diagnosis of oviduct malignancy is possible by vaginal smears when other procedures fail. This patient did not receive definitive therapy on the basis of smear diagnosis, but was operated upon because of continued undiagnosed postmenopausal bleeding, associated with a thickening which suggested a mass in the left adnexal region.

Patient 8 demonstrates the value of the smear in diagnosing sarcoma of the uterus. The original smear diagnosis of adenocarcinoma was due to the lack of sufficient experience in recognizing sarcomatous cells. Malignancy was identified, though not properly classified. This patient also illustrates the use of estrogens<sup>3</sup> to decrease the amount of inflammatory exudate which often masks the epithelial elements in smears.

The smears in patient 9, even when obtained from the tumor surface, failed to show cells which could be called malignant. This instance is reported to show that the smear method of diagnosis is not infallible. Firstly, malignant cells must be present before diagnosis is possible. Secondly, these cells must show the characteristic malignant stigmata. The smears from the tumor surface in this instance contained no malignant appearing cells and furthermore the cells had a less suspicious appearance than did those from other smears which had been confirmed previously as hyperplastic endometrium.

Intrauterine malignancy may be diagnosed by vaginal smears as shown by patient 10.

### Discussion

This manner of diagnosing genital malignancy is relatively simple though not inexpensive when one considers the necessary chemicals and technical aid required. The smears are obtained in a short time, but careful and frequently lengthy scrutiny is necessary for interpretation. Thus, if one allots thirty to forty minutes for obtaining, staining, and interpreting the smears, the final smear diagnosis may be completed within a much shorter time than that necessary to obtain a tissue diagnosis.

The interpretation of vaginal smears is difficult but compares favorably to that of bone marrow differentials. The cyclic changes associated with the menses are interpreted with approximately the same degree of difficulty as in reading a white blood cell differential. Characteristics of cells used in making a smear diagnosis of malignancy are quite similar to the individual cellular changes described by pathologists for the diagnosis of intra-epithelial carcinoma.<sup>5, 6</sup> Pathologists report patients who had tissue changes twelve years prior to the time of invasion.<sup>6</sup> These changes may be detected in vaginal smears. We feel that this work should be under close supervision of a trained cytologist who is capable of rendering expert interpretation.

The diagnosis of malignancy from smears often may be complicated by malignant appearing cells and nuclei which occur in benign conditions.

Extremely large, hyperchromatic, and malshaped free nuclei may appear in smears of patients having a chronic vaginitis. These nuclei are alarming to the inexperienced. Subtle differences in irregularities and pigmentation of the nuclei rule them out as malignant.

Ayre<sup>7</sup> has described certain cells which he believes characterize pre-cancerous changes. These cells are seen frequently in our smears but thus far we have not been able to consider them anything but normal. A discussion of Ayre's "precancerous" cells will appear in a paper to be published by our group. These cells previously have caused us much concern and were a complicating factor in making diagnoses.

Intrauterine cells in instances of incomplete abortion may be confusing if cells characteristic of pregnancy, abortion or post partum state are not present. When pregnancy-type cells are present without evidence of abortion the diagnosis is difficult. The intra-uterine cells causing the difficulty resemble very closely malignant squamous cervical cells. In fact, if one were required to make a diagnosis from viewing only a group of these cells, most probably the diagnosis would be squamous celled carcinoma of the cervix. Such smears will be described by us in a subsequent paper.

The most vulnerable point in this particular field is the diagnosis of adenocarcinoma of the endometrium. We agree with other investigators on this point.<sup>4, 8</sup> It is extremely difficult in many smears to distinguish between the nuclei of hyperplastic endometrial cells and those of a malignant process. This is especially true when large, irregularly shaped, hyperchromatic, free nuclei are present. Under these circumstances, other stigmata of malignancy combined with the experience of the interpreter help to reduce the percentage of error in diagnosis.

Another type of smear which may cause much anxiety to the interpreter is one that shows a pyometra. We know that this often accompanies malignancy of the cervix or corpus uteri. In addition to this clinical knowledge there may be numerous atypical cells which strongly suggest both squamous and adenocarcinoma. When the diagnosis is not clear-cut in such instances, the policy of Papanicolaou is followed. The report is made as doubtful and repeat smears are requested. We agree with Papanicolaou that it is a better practice to be conservative and miss a diagnosis than to brand an innocent one with a malignancy.

Inflammatory processes in general may produce malignant appearing cells. These cells occur often in severe chronic cervicitis, especially when *Trichomonas vaginalis* are present.

Our technic and results are improving in direct ratio to our experience.

This laboratory procedure is rapidly becoming a *must* in the armamentarium of gynecologic studies. The method has important potentialities in screening surveys because of the possibility of earlier detection of cancer than by the biopsy method. We believe that in the future this service can be offered to every physician as are serology examinations at the present time. When this time comes, physicians will be required to do more pelvic examinations when obtaining vaginal smears. The combination of both will result in early detection of malignancies. We will be able then to decrease the death rate in women due to genital cancer.

We wish to emphasize that at the present time we feel that every patient should have pathologic tissue confirmation of smear diagnosis of malignancy before institution of therapy.

### Summary

Six thousand, seven hundred fifty-three smears on 1,709 patients have been studied. The smears were obtained, stained, and classified by the methods of Papanicolaou and Traut. One hundred fourteen patients with genital malignancy were diagnosed by smears out of a group of 124 diagnosed by pathology; a percentage error of 8.1.

False positive diagnoses were made in 34 of 1,585 patients; a percentage error of 2.1.

Nine patients have been presented who illustrate the diagnosis of genital carcinoma by the vaginal smear method. These include squamous celled carcinoma of the cervix, 5; squamous celled carcinoma of the vulva, 1; sarcoma of the uterus, 1; and chorionepithelioma, 1. Those patients having squamous celled carcinoma of the cervix show that the diagnosis of malignancy sometimes may be made earlier by smears than by the biopsy method.

Primary adenocarcinoma of the oviduct was revealed in the vaginal smears of one patient.

One patient with adenocarcinoma of the endometrium in which smears were negative even when they were obtained from the tumor surface is reported to show a weakness of the smear method.

Salient features, good and bad, of the vaginal smear method in the diagnosis of genital cancer have been presented.

It is thought that this procedure will become routine in the complete physical examination of women, but that treatment for malignancy should not be instituted prior to pathologic tissue confirmation.

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## A CRITICAL SURVEY OF THE QUESTIONABLE PELVIS

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WITH the apparent normal implantation of the impregnated ovum, the hazard potential of the gravid state is immediately germinated. Obstetric practice is presuming to acquire more and more the precision of a scientific art. The accuracy of prediction of the mode of delivery is concerned with many factors such as careful anamnesis, with particular emphasis on every phase of previous pregnancies; a complete general physical and endocrinological examination to include special reference to the constitutional habitus; a thorough evaluation of the pelvis in respect to the internal genitals, the fascial supports and the state of the cervix; and, lastly, upon a careful consideration of the bony framework, its special osseous characteristics and essential diameters. The latter, and certainly the most constant factor, presents a real challenge to precision obstetrics in respect to the anticipation of certain mechanisms of labor. It governs one's conduct of a case as regards test of labor, type of forceps used, recourse to internal podalic version and extraction, elective cesarean section, whatever the type, or even the selection of pertinent analgesia or anesthesia. One is constantly striving for the ideal termination of labor, and this paper is intended to present a survey of the factors concerned with such responsibility, and to direct special emphasis to the midplane of the pelvis. For the careful evaluation of this pelvic level one is dependent upon help received from diagnostic roentgen-pelvimetry.

The definition of the normal female pelvis is as elusive as that concerned with any field of medicine, and variations in morphology, however minute, may be innumerable. One is dealing with the mean, rather than the ideal. One's knowledge of the mean diameters is essential to the recognition of the nature of contraction, through the lessening of the essential diameters, of any one plane of the pelvis. The study of measured capacity is that of a fixed factor. One must be cognizant, as well, of others, such as the weight and thickness of the osseous components; any uterine, adnexal, or soft tissue pathology (to include the uterine cervix in the sense of heralding dystocia); the labor pattern and the nature of the expulsive forces; the degree of moldability of the cranial bones in determining the adaptability of the head to the pelvic contours; the flexibility of the pelvis as regards the ligaments and fascia; and the size and weight of the infant. These latter are, as it were, the insensible factors, and escape the precision that is desirable in the study of the clinical suspect pelvis. One's own observations tend to support the association, as quoted by Kenny,<sup>37</sup> of such workers as Caldwell and Moloy, Fishberg and Thoms, of physical characteristics versus pelvic types. These studies are worthy of review.

Of the various attempts at classification of pelvises, the Caldwell-Moloy presentation of the gynecoid, android, anthropoid, and platypelloid types appears

to be workable and practicable. The characteristics of these various types, however variable, are now well recognized. No discussion of this sort can be complete without studying most carefully the work of Thoms and his associates.<sup>55-63</sup> In the normal gynecoid pelvis, the anteroposterior, transverse, and posterior sagittal diameters of the inlet are given respectively as 11.5 cm., 13 cm., and 4 cm. The above diameters, as applied to the midplane (the plane passing from the inferior margin of the symphysis pubis through the ischial spines usually to the juncture of the fourth and fifth sacral segments) are 11.5 cm., 10.5 cm. (interspinous) and 5 cm. The biischial (at a level just above the tuberosities) and posterior sagittal diameters of the outlet average 10 cm. and 8.5 cm., respectively.

Although one may acquiesce to the above parent forms, one is impressed with the relatively high incidence of variability; the true incidence, particularly of the mixed types, is thus difficult to ascertain. This difficulty is somewhat obviated by the attitude of Caldwell and co-workers<sup>11</sup> of having the first or essential feature refer to the nature of the posterior pelvis, and the lesser-pronounced characteristic governed by that of the anterior segment. They describe five mixed types: the anthropoid-gynecoid, the gynecoid-flat, the android-anthropoid, the android-flat, and the android-gynecoid. It is difficult many times to indicate the variables so simply. This is especially true of the variable relationships between the base characteristics and position of the spines, in the coronal plane (as indicated by the length of the posterior sagittal), and the attitude of the lateral walls. The funnel character, not infrequently seen, may be real or inverted. Thus it may be emphasized that neither the inlet morphology nor the outlet configuration are truly indicative of the spatial features present in the midplane. Herein presents the weakness of clinical mensuration except that one, by careful palpation of every component part of the midpelvic plane, may be suspicious of any of the above-stated departures from the ideal. The roentgenologist is then called upon to indicate the degree of deviation from the normal.

Admitting that much essential information may be gained from a thorough clinical study of the female pelvis, and appreciating at the same time its limitations, one must acknowledge accessory aid from roentgenologic interpretations. One may rightfully state that the midplane is obstetrically a most important pelvic level as regards ultimate fetal salvage. Such study is indicated in:

1. The clinical suspect pelvis, to include all planes.
2. The primigravida with an unengaged head, especially in occiput posterior position, whether or not accompanied by an extension attitude; and especially if attended by a definite overriding with the patient in an extreme lithotomy position.
3. A history of serious dystocia during previous labors, eventuating especially in a mutilated or stillborn fetus.
4. Malpresentation in the elderly primigravida.
5. A history of previous fracture or bony disease of the pelvis. In these instances the inlet, as well, might be suspected.

Granted the fulfillment of the foregoing indications, what have the stereos and isometric roentgenograms to offer the accoucheur? Knowledge is given as to:

1. The general morphology, to include the mensuration of the essential diameters and the variations of the pelvic shape.
2. The nature and degree of contraction present. In such manner this study may be utilized as well in prognosticating the mechanism of labor.
3. The depth of engagement of the presenting part, as suggested by McLane,<sup>40</sup> with a note as to the clearance, the character of the sciatic notch, the inclination of the symphysis, the sacral characteristics, the depth of the posterior pelvis, and, in cases of true transverse position, the biparietal diameter of the fetal head.

TABLE

PELVIC PLANES	400 CONSECUTIVE CASES (CROSS-SECTION OF REFERRED CASES) AUTHORS	AVERAGE MEAN DIAMETERS OF PATIENTS WITH NORMAL DELIVERIES	
		WEINBERG AND SCADRON	SELECTED CASES AUTHORS
		Sums	Sums
<i>Inlet:</i>			
Conjugata vera	11.40 cm.	25.10 cm.	11.77 cm. (11.88 cm.) †
Transverse Area (Allen)	13.70 cm. 122.3 sq. em.	24.80 cm.	13.12 cm. 121.0 sq. em. (126.7 sq. em.)
<i>Midplane:</i>			
Anteroposterior	11.68 cm.	21.94 cm.	11.76 cm. (11.41 cm.)
Interspinous	10.26 cm.	14.10 cm.	10.53 cm. (10.30 cm.)
Posterior sagittal	3.84 cm.		4.10 cm. (4.03 cm.)
Area (Allen)	94.4 sq. em.		97.0 sq. em. (91.7 sq. em.)
<i>Outlet:</i>			
Anteroposterior	11.68 cm.		11.68 cm. (11.41 cm.)
Biischial* (Bituberous)	8.66 cm.	16.82 cm.	9.42 cm. (11.13 cm.)
Posterior sagittal	8.16 cm.		7.98 cm. (7.09 cm.)

\*Our transverse measurement was taken from the bases of the pubic arch and does not represent the wider biischial diameter. Our mean biischial diameter was computed as 11.54 cm.

†The figures in parentheses are those of Ane and Menville, and were derived from a study of 450 cases.

4. Multiplicity and attitudes of the various passengers.
5. Advisability of allowing a test of labor.
6. Viability of the fetus.
7. After the onset of labor, one may note the degree of molding, of lateral flexion, change in station, and the adaptation of the fetal head to the pelvis.

How may one recognize the contracted pelvis? One may think of any deviation from the normal in respect to a lessening of the *mean essential diameters* as an indication of contraction. The incidence and nature of the contracted forms are given in papers by Caldwell and Moloy,<sup>6-12</sup> Eller and Mengert,<sup>17</sup> Johnson,<sup>32-35</sup> Kenny,<sup>37</sup> Judson,<sup>38</sup> Ane,<sup>4</sup> Hennessy,<sup>23</sup> and Danforth.<sup>13</sup>

Appreciating the factor of relative degree of pelvic contraction, it might be well to combine such a discussion with that of prognosis of delivery, both before and after the onset of labor. It must be remembered that by the study of the inlet morphology alone, many contracted forms may be overlooked. Moreover, as Steele and Javert have shown,<sup>51-54</sup> the anteroposterior and transverse diameters are hardly a true index of morphology or volumetric capacity, whether of the pelvic brim or any other plane.

The stereoradiographic study will, however, reveal the true morphology or volumetric capacity of the inlet, with its essential diameters. A determination of the transverse diameters (transverse of the inlet, interspinous, biischial or bituberous, and the base of the pubic arch), the splay of the side walls, the width of Michaelis' rhomboid, and the characteristics of the spines and subpubic angle should be made. The lateral view should include the exact measurements of the conjugate vera; the anteroposterior diameters from the symphysis to both the sacral and coccygeal tips; the depth of the pelvis; the inclination of the pelvic brim; the characteristics of the symphysis and sacrum;

## I

HODGES AND DIPPEL SUSPECT PELVES		GRABER AND KANTER	
		BORDERLINE CONTRACTIONS	ABSOLUTE CONTRACTIONS
10.50 cm.	<i>Sums</i>	8.0-9.5 cm.	8.0-8.5 cm.
13.50 cm.	} 24.00 cm.		
111.0 sq. em.			
11.5-12.0 cm.			
10.5 em.	} 22.0-22.5 em.		
4.0 em.	} 14.50 em.	8.0-9.5 cm.	8.0 em.
94.5-98.7 sq. em.		4.0-3.5 cm.	3.0-3.5 em.
11.5-12.0 cm.			
10.00 em.	} 16.0-17.0 em.	8.5-9.0 cm.	8.0 em.
6.0-7.0 cm	}	6.0 cm.	5.0 em.
		14.5-15.0 em.	13.0 em.

the amount of free space between the fetal head and inlet; the nature of the sacrosciatic notch; and, in the case of the true lateral view of the fetal head, its biparietal diameter.

Our experience is in agreement with the stated fact that actual contraction is less frequent than diagnosed clinically. Granted that the morphologic features of all pelvises are essential to the understanding of volumetric capacity, a definite practical application of vital diameters is acceptable. It is particularly applicable in aiding more accurately to visualize that most important part of the obstetric pelvis, the posterior segment, and its counterpart, compensatory space. To illustrate certain salient features of the suspect pelvis, the following table presents a summary of inlet, midplane, and outlet measurements, as seen in the normal, borderline, and contracted pelvis.

Table I would seem to indicate that major thought was directed to the midplane in that the sums of the essential diameters and the area values of the inlet, in our cross-section of referred cases of, respectively, 25.10 cm. and 122.3 sq. cm., agree favorably with those of 24.89 cm. and 121.5 sq. cm. in the spontaneous deliveries. The sums of the anteroposterior and the interspinous diameters of the former agree most closely to those of the suspect pelvises of our selected cases, and to those of Hodges and Dipple.

The precision evidence that is made possible by present methods of roentgenpelvimetry should permit some ease and certainty of prognosis of labor. Granted that a comprehensive impression of the pelvis is important, the study should be further broken down in the manner of individualizing each plane. Even then, errors of prognosis are possible. Williams<sup>67</sup> has stated that difficulty is often anticipated where none is encountered; and, conversely, dystocia is rarely experienced when none is prognosticated. Jacobs,<sup>28, 29</sup> Ane and Menville, Klingensmith and Barden<sup>38</sup> entertain an interesting discussion as to prognosis. Only the android forms with a conjugata vera as little as 10.00 cm. are associated with a high incidence of cesarean section. A conjugata vera of 11.00 cm. in this

group may be expected to admit the cephalus. A trial of labor is permitted in the contracted pelvis with a c.v. of 8.0 to 10.0 cm., provided that the presenting part can be pushed within 1 cm. of the spines.

It seems fair to state that where one has a combined conjugata vera and transverse inlet sum of less than 23 cm. and/or a combined interspinous and posterior sagittal midplane sum of less than 14 cm., a dystocic labor may be expected. With an inlet sum as low as 23 cm. and a midplane sum of 15 cm. or more, a trial of labor is justified. A test of labor is permissible in an anticipated mild dystocia of the inlet, in the platypelloid (especially with inverted cone characteristics) or other type of pelvis, where the midplane or outlet diameters may be considered adequate. Surgical induction in such questionable cases is attended by too great a risk, and the problem of elective cesarean section in the presence of antepartum rupture of the amnion becomes real. Weinberg and Seadron<sup>65</sup> have presented an interesting table which may be accepted as workable in respect to inlet pelvimetry as a basis for prognosis. In patients requiring cesarean section, the sum of the interspinous and transverse diameters averaged 23.3 cm. They added that spontaneous deliveries do occur with sums of 22 to 24 cm., and that one may allow a test of labor with values as low as 20 to 22 centimeters. Caldwell and Moloy have postulated that the prognosis of a high head is better if it lay over the posterior segment than if over the anterior. The antithesis is true in the case of the midplane.

In concluding this discussion of the inlet, it might be added that the unengaged head at term, in addition to the suspect pelvis, becomes of significance in respect to the suspect placenta as well as the suspect fetus. In the presence of normal inlet measurements and the inability to force the head into this plane in the extreme lithotomy position, one must exclude the symptomless placenta previa, preferably by a soft-tissue x-ray; also, abnormality of the fetus, inherent or attitudinal; the presence of retroperitoneal solid tumors; and bony disease of the pelvis. The presence of any such adverse factor, especially in the elderly primipara with a posterior or hyperextension attitude, and a long, conical, rigid cervix; or in the multipara with a history of difficult forceps and stillbirth, natural or imposed, should suggest the performance of a cesarean section.

With the head well engaged, either before or after the onset of labor, one's attention is then directed to the midplane, the plane of least pelvic diameters. A midplane contraction should be suspected if any one or more of the following conditions accrue:

1. A constitutionally male type of patient.
2. A diagnosis of an android pelvis or android modification of other pelvic forms clinically, and supported by roentgen morphologic study. It is interesting to note that in difficult labors the incidence of android characters is a third greater than in an unselected group.
3. Prominent and close spines, as determined by palpation.
4. Contracted outlet in the presence of a narrowed forepelvis and subpubic angle, and a flat sacrum. It is commonly appreciated that transverse contraction of the midplane is often associated with a narrow, angulated, and obstetrically useless forepelvis.
5. Premature rupture of membranes.
6. Malposition, especially as refers to transverse and posterior arrests, with or without full dilatation. Figures for this plane in the normal, borderline and absolute contracted forms have been presented in the foregoing table.

The interspinous diameter is most important but an attending compensatory space may be influenced by the splay of the side walls; the antero-posterior and posterior sagittal diameters; and by the characteristics of the sacrum and the sacrosciatic notch. McSweeney and Moloney<sup>41</sup> found the interspinous diameter greater than 9.0 cm. in 84 per cent, 9.0 cm. or less in

15 per cent, and less than 8.0 cm. in 1 per cent of cases. They anticipate dystocia where the posterior sagittal is less than 3.5 cm. In Ane and Menville's series, 52 of 61 cases with a contraction of 10 mm. or more, in one or more diameters, required an operative delivery.<sup>4</sup> Of 44 patients where the interspinous or biischial diameters were reduced 10 mm. or more, only 3 to 7 per cent delivered normally. Guerriero and associates<sup>22</sup> anticipate dystocia where the conjugata vera is less than 9 cm. and the sum of the interspinous and posterior sagittal diameters is less than 13.5 centimeters. Weinberg and Seadron<sup>67</sup> place the latter value at 13.0 cm. Our figures tend to support the latter authors. Weinberg and Seadron also state that midforceps extractions are common with a summary measurement directed toward 14.0 cm. from the normal; that delivery from below is rarely accomplished with a value of 13.5 cm. or less; and almost never when the figure becomes 13.0 or less. As may be noted below, our experience has not proved to be quite as severe as this. The discrepancy may be explained by the fact that our sacral end point almost always falls nearer the junction of the fourth and fifth sacral segment, rather than at the tip of the sacrum. A midplane sum of 14.9 was common to their mid-forceps and one of 13.0 to the section cases.

A different approach to this problem by our English confreres is worthy of note. Williams and Phillips<sup>67</sup> employ lateral and frontal projection charts, a method that permits them a most favorable prognosis percentage. Nicholson and Allen,<sup>45</sup> working with the square root of the product of two essential diameters, arrived at a workable formula for determining the area of each pelvic plane in square centimeters. Allen,<sup>1, 2</sup> whose table of prognosis is most workable, may be commended for his application of this scheme. A conjugate of 10.3 cm. or less portends an abnormal labor, and a normal labor is assured with one of 13.7 cm. or greater. The critical level for the conjugate is given as 11.4 cm., and that of the transverse is 12.3 cm. If either the conjugate or the brim area is reduced to 105 sq. cm. or lower, one should consider the possibility of delivery by cesarean section. Such a termination becomes a decided probability if reduced to 90 sq. cm. A normal delivery is assured with a value of 130 sq. cm. or more.

In his study of the midplane, Allen gives the critical levels of 11.3 cm. and 9.5 cm. for the anteroposterior and interspinous diameters, respectively. Our experience is in agreement with his statement that if the interspinous is the critical diameter, one would expect more arrests with the above critical level than we have encountered. He, therefore, makes use of a transverse diameter taken between the flat opposing surfaces of the ischia anterior to the bases of the spinous processes. This diameter's critical level is 10.9 cm. This becomes important as an index of anterior compensatory space if the interspinous is less than 10 centimeters. The critical area level is 90 sq. cm., using the interspinous diameter, and 104 employing the transverse. Ince and Young<sup>27</sup> feel that normal delivery is possible at an 85 sq. cm. level. Williams and Phillips<sup>67</sup> suggest that the prognosis is serious if the anteroposterior and interspinous are less than 10.1 cm. and 9.6 cm., respectively. Allen, concurring with the above, states that a vaginal delivery becomes uncertain with an area value of 85 square centimeters. Using the bispinous diameter instead of the transverse, this figure becomes 10 to 15 sq. cm. less, or 70 to 75 square centimeters. He maintains that a normal delivery is almost certain with an area of 110 sq. cm. and an interspinous of 10 centimeters. Allen's article presents a workable table of prognosis in concentrating on area values for the various planes of importance.

In the last of the pelvic planes to merit discussion, the outlet, interest is directed mainly to the angle and nature of the pubic arch; the characteristics of the fascial pelvic floor; the thickness of the perineal body; and the pubo-sacral, pubococcygeal, biischial, and posterior sagittal diameters. Williams and

TABLE II. AVERAGE MEAN DIAMETERS IN CENTIMETERS AND TERMINATION OF LABOR

PELVIC PLANES	SPONTANEOUS DELIVERIES	OPERATIVE DELIVERIES (CESAREAN SECTIONS INCLUDED)	CESAREAN SECTIONS	MIDPLANE ARREST		MIDPLANE CONTRACTION WITH SPONTANEOUS OUTCOME	MIDPLANE ARREST REQUIRING OUTLET FORCEPS	Sums†
				Sums*	MIDPLANE ARREST			
<i>Inlet:</i>								
Conjugate vera	11.77 {	11.32 {	10.76 {	12.03 {	11.34 {	11.60 {	11.47 {	25.07
Transverse	13.12 {	12.96 {	12.46 {	12.95 {	12.62 {	13.47 {	11.70	
Inlet Area (Sq. cm.)	120.9	115.0	105.7	112.0	111.4			
<i>Midplane:</i>								
Anteroposterior	11.76 {	22.29 {	10.86 {	11.50 {	11.14 {	11.15 {	10.16 {	21.31
Interspinous	10.53 {	14.63 {	8.95 {	9.90 {	9.53 {	10.16 {	3.33	
Posterior sagittal	4.10	3.68	2.74	3.54	3.28	12.81		
Midplane Area (A.P. + I.S.)	97.0	89.3	76.4	89.0	82.6	89.4		
<i>Outlet:</i>								
Bituberous (End point is base of pubic arch)	9.42 {	9.11 {	8.78 {	9.11 {	9.06 {	10.06 {		
Posterior sagittal	7.98 {	7.64 {	7.49 {	7.62 {	7.59 {	6.87 {		

\*Mean average weight of babies represented in this group = 3563 Gm.

†Mean average weight of babies = 3125 Gm.; Mean average time of labor = 15 hours.

‡Mean average weight of babies = 3517 Gm.; Mean average time of labor = 41.5 hours.

Phillips<sup>67</sup> stressed the anteroposterior and interspinous diameters of the outlet. The former may be as little as 9.5 cm., and the latter 9.14 cm. without resulting in an arrest. An interspinous of less than 9.64 cm. associated with an anteroposterior of less than 10.15 cm., along with a narrow arch, may prove serious. The discussions in this vein, of Ragan,<sup>47</sup> Williams,<sup>66</sup> Walsh,<sup>64</sup> and Eller and Mengert<sup>17, 18</sup> are worthy of review.

From a diligent study of the influential accessible factors as described above, one may attempt, in the individual case, to prognosticate the mechanism of labor to follow. The inaccessible factors come into play with the onset of labor. With experience, the size of the baby may be estimated with some degree of practicability. In the contracted pelvis, with a minor reduction in any of the mean diameters of any one plane, a baby of less than 3,200 to 3,300 Gm., with average forceful pains and moldability of the head, with or without the aid of forceps, should deliver. In the case of cephalopelvic disproportion at the inlet, with progressive limitation of space in successive planes, a test of labor is unwarranted.

For the sake of brevity, the study of mechanism of labor as presented by Barnes, Caldwell and co-workers, has reluctantly been excluded from this discussion. Suffice it to say, where an arrest is encountered, in the android, android-gynecoid, and android-antrhopoid pelvis, rotation in the plane of arrest should be attempted, but not forced. One may have to resort to traction with low rotation, high manual rotation with subsequent forceps extraction, or internal podalgie version with breech extraction. In the case of transverse arrest, especially in the platypelloid pelvis, the head may have to be brought down, with or without lateral flexion, and rotated under the pubic arch. If the converging sidewalls are crowded by narrow spines, rotation to an oblique position should be effected before traction is applied. Once the cephalus has reached the bony outlet, delivery may be completed without difficulty.

The tables to follow are intended to reveal the mean diameters and area levels found in the conditions alluded to therein. Table II represents a cross section of cases in general.

From the study of this table, one will note that no difficulties were encountered with the values revealed in column one. Although open to some question, operative deliveries were performed in the presence of apparently normal measurements, as represented in column two. It is in this group that the incidence of cesarean section can be reduced. The sections, as shown in column three, are justified. Midplane arrests may be anticipated with babies weighing 3,563 Gm., with the summary values of the midplane of 21.4 cm. and 13.44 cm. for the anteroposterior and interspinous diameters, respectively, and 89 sq. cm. for the area value. Column six suggests that these labors may be allowed to progress in anticipation of merely performing a delivery by outlet forceps. Column five offers some assurance that a spontaneous outcome is possible for a baby weighing 3,125 Gm., with midplane summary values of 20.67 cm. and 12.81 cm., and an area of 82.6 square centimeters.

Table III concerns the inlet, and the cases represented therein are broken down according to the degree of contraction present.

In the foregoing table, four patients of Group II-A with a combined average mean of 24.37 cm. had a complicating toxemia. They might have been allowed a test of labor. Cesarean section was done in two cases of Group II-B after six hours of no progress, with membranes ruptured.

In studying Table III, the following features are noted:

1. All deliveries were understandably operative in Groups I-A and I-B.
2. Decision as to elective section may be questioned in Groups II-A, III-A, and eight of the cases included in IV-A.
3. The intrapartum cesarean sections require no explanation.

TABLE III. EFFECT OF INLET CONTRACTIONS

INLET DIAMETERS (IN CMS.)	A. ELECTIVE CESARIAN SECTION*	B. INTRAPARTUM CESAREAN SECTION†	C. HIGH FORCEPS‡			LOW FORCEPS			D. SPONTANEOUS DELIVERIES¶
			Sums	(5 cases)	Sums	(2 cases)	Sums	(1 case)	
I. Conjugate vera under 10:									
Conjugate vera	(7 cases) 9.39 12.79 94.2	(5 cases) 22.18 11.60 98.1	Sum	10.80 11.60 98.1	Sum	9.30 12.25 89.6	Sum	9.60 13.60 102.0	Sum
Transverse Area (in sq. cm.)									
II. Conjugate vera 10-10.5:									
Conjugate vera	(10 cases) 10.25 12.47 110.8	(3 cases) 22.72 12.28 99.2	Sum	10.27 12.70 101.0	Sum	22.55 12.70 (Axis traction)	Sum	22.90	Sum
Transverse Area									
III. Conjugate vera 10.5-11:									
Conjugate vera	(7 cases) 10.67 13.23 110.6	(3 cases)†† 23.90 12.70 106.4	Sum	10.70 12.70 106.4	Sum	10.72 12.37 103.9	Sum	23.09 12.20 101.3	Sum
Transverse Area									
Midplane sum									
IV. Conjugate vera over 11, but a combined c.v. and tr. under 24									
Conjugate vera	(10 cases)***								
Transverse Area									
Midplane sum	11.43 12.14 108.9	23.57	Sum	11.33 12.13 107.1	Sum	23.46 13.77 (2 axis traction)	Sum	11.33 12.13 107.1	Sum
V. Conjugate vera over 11, but a combined c.v. and tr. over 24									
Conjugate vera									
Transverse Area									
Midplane sum									

\*The mean average weight of babies in this group (A) were: I, 3,376 Gm.; II, 3,300 Gm.; III, 3,370 Gm.; and IV, 3,307 Gm.

†Mean average baby weight and mean average hours of labor were (B): I, 3,737 Gm., 12 hrs.; II, 3,538 Gm., 5 hrs.; III, 3,606 Gm., and 41 hrs.

‡Weight and hours here were (C): I, 3,375 Gm., 17 hrs.; II, 3,368 Gm., 18.5 hrs.

§Weight and hours here were (O): I, 3,280 Gm., 13 hrs.; III, 3,485 Gm., 45 hrs.; IV, 3,401 Gm., 24 hrs.

||Weight and hours here were (C): I, 2,900 Gm., 14 hrs.; III, 3,410 Gm., 39 hrs.

¶Weight and hours of this group were (D): II, 3,085 Gm., 15.3 hrs.; III, 3,585 Gm., 14.5 hrs.; IV, 2,435 Gm., 14 hrs.; and V, 3,587 Gm., 12 hrs.

\*\*Included here (A) were 1 breech, 6 midplane contractions, and 1 previous cesarean section.

††Included (B) 1 brow presentation, Wt. 4,048 Gm.

#There was one case with prolapsed cord; normal sums are not included. Those with normal midplane sums are not included in this group (C).

§§The figures in parentheses represent sums of anteroposterior and interspinous, as compared with the midplane sum of the interspinous and posterior sagittal diameter.

4. The relatively high incidence of forceps deliveries in Groups II-C, III-C, and IV-C are accounted for, in some instances, by an accompanying midplane crowding, as an expression of android and small gynecoid characters. These modifications, which did not apply to the spontaneous deliveries, are revealed in the numbers in parentheses. These numbers represent the sums of the antero-posterior and transverse diameters of the midplane.

5. Added deductions are included in the discussion of the paper.

Table IV represents an analysis of midplane contractions according to degree, and the types of deliveries that eventuated.

### Discussion

A review of the literature and a careful analysis of our own work in the study of the suspect pelvis would seem to indicate that, although great strides have been made toward the proper conduct of labor, even greater success is possible. The roentgenologist is in the position to offer us reasonably accurate and dependable precision data. This may still be regarded as an accessory aid, and is secondary to one's obstetric judgment. A meticulous study of each individual plane is mandatory.

The incidence of contracted forms has been given as 8.3 to 25.1 per cent; the greater number conforming to the platypelloid, small gynecoid, and the android types; and the least to the anthropoid configuration. In this series of cases, the end points being similar to those of Hodges and Dipple, the mean true conjugate vera was 11.4 cm., the transverse 13.7 cm., and the sum of the two was 25.1 centimeters. For the spontaneous deliveries, these values were respectively 11.77 cm., 13.2 cm., and 24.89 centimeters. The corresponding values for the contracted pelvis were found to be significantly lower, and are represented in Tables III and IV. The pelvic inlet plane area for the spontaneous group is given as 121.96 square centimeters. The critical level appears to be 115 square centimeters. Vaginal delivery is uncertain where the value is less than 90 square centimeters, and the possibility of cesarean section must be considered when this figure approaches 105 square centimeters (Allen).

In respect to the midplane in this "suspect" classification, the values for the anteroposterior, the interspinous, and the posterior sagittal are, respectively, 11.76 cm., 10.53 cm., and 4.10 centimeters. The sum of the former two is 21.94 cm., and of the latter two, 14.62 centimeters. The plane area is 98.20 square centimeters. The critical level for the transverse of Allen is 10.9 centimeters. Allen, using his transverse component, places the critical level at 104 sq. cm., or 90 sq. cm., using the interspinous diameter. According to him, vaginal delivery becomes uncertain at a value of 85 sq. cm. (70 to 75 sq. cm. employing the interspinous diameter), and the prognosis is serious if the figure is 76 sq. cm. or less. Vaginal delivery is almost certain when the area proximates 110 sq. cm., and the interspinous is 10 centimeters. To this, our experience seems to agree.

As regards the outlet, the average pubic bituberous (the end points located at the base of the pubic arch) is 8.66 cm.; and the posterior sagittal is 8.16 cm., thus giving a sum of 16.82 centimeters. Allen found that a posterior sagittal of 4.8 cm. or less offered a poor prognosis. A value of 6.5 cm. would suggest a normal delivery.

Since this series represents cases in which the referring clinician suspected some degree of cephalopelvic disproportion, the values may be considered a mildly critical level for the plane concerned, at or above which a spontaneous delivery may be anticipated.

Our findings for the inlet plane (Table III) support the implications as set forth in the table of Weinberg and Seadron, modified to include Allen's area computations.

TABLE IV. EFFECT OF MIDPLANE CONTRACTIONS

MIDPLANES IN DIAMETERS (IN CMS.)		A. ELECTIVE CESAREAN SECTION*	B. INTRAPARTUM CESAREAN SECTION†	C. FORCEPS DELIVERIES‡	D. SPONTANEOUS DELIVERIES§
		(27 cases)	(2 cases)	(17 cases)¶	(3 cases)
I.	Interspinous plus posterior sagittal under 13.0:				
Anteroposterior	11.07	{ 20.16	11.20	11.07	11.53
Interspinous	9.09	{ 12.12	9.85	9.29	9.30
Posterior sagittal	3.03	{ 2.85	12.70	3.05	3.27
Area (in sq. cm.)	79.1	68.2		80.8	83.8
II.	I.S. plus P.S. 13.1-13.6:				
Anteroposterior					
Interspinous					
Posterior sagittal					
Area					
III.	I.S. plus P.S. 13.6-14.1:				
Anteroposterior	11.50	{ 21.78			
Interspinous	10.28	{ 13.66			
Posterior sagittal	3.38	{ 94.7			
Area					
IV.	I.S. plus P.S. 14.1-14.6:				
Anteroposterior	11.40	{ 21.40			
Interspinous	10.00	{ 14.10			
Posterior sagittal	4.10	{ 88.3			
Area					
V.	I.S. plus P.S. over 14.6:				
Anteroposterior					
Interspinous					
Posterior sagittal					
Area					

\*The mean average weight of babies in this group (A) were: I, 3,375 Gm.; III, 3,495 Gm.; IV, 3,390 Gm.

†Mean average baby weight and mean average hours of labor (B) were: I, 3,964 Gm., 5 hours; II, 4,048 Gm., 5 hrs.

‡Weight and hours here (C) were:

I, 3,514 Gm., 27 hrs.; II, 3,585 Gm., 18.3 hrs.; III, 3,616 Gm., 38.2 hrs.; IV, 3,456 Gm., 26.5 hrs.; and V, 3,687 Gm., 18 hrs.

§Weight and hours here (D) were: I, 3,173 Gm., 14 hrs.; II, 3,480 Gm., 14 hrs.; III, 3,590 Gm., 16 hrs.; IV, 3,572 Gm., 26 hrs.; and V, 3,350 Gm., 18.5 hrs.

||In this group (C), 8 were axis traction, 4 midforceps, 4 essential low forceps, and 1 breech.

¶These (C) included 3 axis traction, 2 midforceps, and 2 essential low forceps.

\*\*Here, (C), 2 were midforceps, and 2 were axis tractions, 2 midforceps, and 1 high midforceps.

††Among these, (C), 2 were axis tractions, 2 midforceps, and 1 breech.

#These (C) represented 4 midforceps, (3 being posteriors), and two essential low forceps.

Criticism for resorting to elective cesarean section for suspected contracted pelvis in ten cases with an inlet sum of 22.72 cm. (baby's weight 3,300 Gm.), another with a sum of 23.90 cm. (3,370 Gm.), and five cases with a sum of 26.30 em. (3,587 Gm.), is likely justified. In those instances of unengaged heads at term, with an inlet mean diameter of 9.39 cm., and a combined anteroposterior and transverse of 22.18 cm., a cesarean section was justifiably indicated.

In this group of patients there were three placenta previas, three with a history of previous sections, one deformed pelvis, one antenatal rupture of the uterus (endometriosis), and five toxemias. There was one stillborn fetus. Although the fetus weighed only 2,300 Gm., the pelvis was one of severe justominor type.

Our experience is in agreement with the impression of Weinberg and Seadron, and of Guerriero, in respect to the critical midplane sums of 13.0 and 13.5 cm., as indicated in sections I-C, II-C, and III-C of Table IV. It is important to state, perhaps, that these patients were delivered as soon as dilatation was complete. Of late, the incidence of midforceps application has been materially reduced by the practice of giving minute doses of pituitrin at the time of delivery. The cases included in section IV-C might have been reduced to a low forceps termination in such manner. It is of significance that areas recorded in sections I-C and II-C were below the critical areas.

Axis traction was resorted to, in many cases, by reason of anticipating a more desirable directional force where traction with other types of forceps seemed a little forced. With our present knowledge, the cases indicated in section III-A (Table IV) could well be permitted a trial of labor. The patients shown in sections I-C, II-C, and IV-A suffered a definite arrest in labor. As will be noted, forty-six operative deliveries were experienced with a midplane sum of less than 13.0 cm., namely: 27 elective sections (3,375 Gm.); 2 intrapartum sections (3,964 Gm.); and 17 fairly difficult forceps deliveries (3,514 Gm.). However, three patients with a mean area of 83.8 sq. cm. (section I-D) delivered spontaneously of babies with a mean average weight of 3,173 Gm. In this series there was only one stillbirth encountered, and in no instance was there any significant maternal or permanent fetal injury sustained. One may readily understand the reasons for spontaneous outcome in sections I-D, III-D, IV-D, and V-D. The sums of the anteroposterior and the interspinous diameters ranged from 23.54 cm. to 20.36 cm. in the operative cases. The real critical level appears to be about 21.5 centimeters. The critical area values of 81.0 sq. cm. (3,500 Gm.) to 91.0 sq. cm. (3,600 Gm.) agree favorably with those in Allen's critical range.

Some difficulty was met with midplane sum means of 13.53 cm., 14.30 cm., and 15.63 cm. (babies of 3,585 Gm., 3,456 Gm., and 3,687 Gm.). In these instances, other factors, such as moldability, poor uterine contractions, and interference early in the second stage of labor may have been in foree. The mean areas were 85.9 sq. cm., 102.0 sq. cm., and 107.2 sq. cm. One may summarize that the critical level remains between 13.0 em. and 13.5 em., and the critical area about 90.0 sq. em. for a 3,300 to 3,600 Gm. baby.

Knowledge gained from surveys of this type should prove very helpful in evaluating the clinical-suspect pelvis, and in exercising the proper conduct of labor in the particular case. A consideration of the importance of the widest transverse diameter in conjunction with the anteroposterior diameter as concerns the midplane (compared to the sum of the latter and the interspinous measurement) is now being conducted in current studies. It is anticipated that the incidence of operative deliveries, to include cesarean sections, will be further reduced.

### Summary

Precision obstetrics is within the scope of practicability. A careful survey of the female pelvis allows for recognition of absolute or relative cephalo-

pelvic disproportion, and should serve to stimulate more precise evaluation of the classification, essential diameters, and areas in square centimeters, of each plane of the pelvis.

Midpelvic contractions, if present, should be suspected, even in the presence of normal inlet and outlet measurements; and these cases should merit the advantages offered by stereo- and isometric roentgenpelvimetry. If clinical measurements of this plane are found to be critical, significant midpelvic disproportion is highly possible.

Election of the proper procedure for the termination of the full-term pregnancy, and prediction of the course of labor may be made with a reasonable degree of accuracy.

With an average size baby, in the absence of unequivocal cephalopelvic disproportion, and under the "permissive" conditions outlined above in respect to the degree and nature of contraction, the patient may, under careful supervision, be allowed to go into labor spontaneously.

No single diameter, except possibly the conjugate vera, should be employed alone for the prognosis of labor.

In considering the sums of any two diameters, that of the widest possible transverse diameter and the anteroposterior diameter might well be combined with the area computation for the fullest measure of efficiency. The latter consideration, emphasizing the presence or limitation of compensatory space, proves the importance of stereo-perspective and classimetric knowledge of the particular pelvis; and appears more significant than a study of the sum of the interspinous and posterior sagittal diameters.

The proper clinical roentgenometric approach to the suspect pelvis promises a favorable advance in lessening maternal morbidity and mortality, a greater fetal salvage, and a lesser incidence of elective cesarean section.

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## TECHNIQUES FOR ISOLATION, MAINTENANCE, AND MASS CULTURE OF DÖDERLEIN'S BACILLUS\*

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(From the Ortho Research Foundation)

SINCE the initial observations regarding the incidence of gram-positive rods in the vagina and the description of these bacteria by Döderlein,<sup>1</sup> a group of organisms now referred to as "Döderlein's bacillus" has come to be used in clinical parlance as one criterion of normality of the human vagina. As such, these bacteria occupy a unique position. Since the low pH of the vaginal fluids in a clinically normal woman has been attributed by Cruickshank and Sharman,<sup>2</sup> Cruickshank,<sup>3</sup> Rakoff<sup>4</sup> to the metabolism of this organism, the solution of numerous problems in its physiology becomes of paramount importance both to the gynecologist and the physiologist, not to mention workers<sup>5-7</sup> in the field of endocrinology. There remains an open question regarding the precise rôle of these gram-positive rods in establishing and maintaining the low pH (1.0 to 5.5) of the so-called "normal" vagina. These problems may well be resolved in part by attempts to study the physiology of the organism in pure culture.

Unfortunately, workers<sup>8, 9</sup> in this field have encountered difficulty in isolating these bacteria from mixed cultures and maintaining them for an extended time on any of the known media combinations.

Cruickshank<sup>10</sup> proposed the use of lactose or glucose hormone agar with 5 per cent defibrinated rabbit blood for the primary isolation of the Döderlein bacilli. It was relatively easy for him to isolate this organism when a Grade I flora existed. However, he encountered difficulty in isolating the bacillus in the mixed culture of a Grade II flora.

Brown and Redowitz<sup>11</sup> adopted whey agar for isolating and maintaining cultures of the vaginal bacillus. The organisms grew poorly at first but apparently adapted themselves to this medium after frequent transfers.

Tomato juice agar, a medium described by Kulp,<sup>12</sup> has given favorable results for the isolation of *Lactobacillus acidophilus*. Weinstein et al.<sup>13</sup> added yeast extract to this medium for the isolation of Döderlein's bacillus.

The purpose of this study was to find an improved medium which would successfully maintain these vaginal bacilli in prolonged culture and provide a possible harvest of mass cultures. It was felt that, if this could be accomplished, the first step toward a program of investigation leading to an understanding of these gram-positive rods and their relation to their natural habitat would have been accomplished.

\*The author is greatly indebted to Dr. Mortimer Speiser and Dr. Heinz Luschinsky of Bellevue Hospital for their assistance in obtaining vaginal cultures.

The blood serum used in this study was obtained through kindness of the staff of the State of New Jersey Department of Health, Trenton, New Jersey.

### Materials

Nine cultures were included in this study. Five of these were isolated from patients in the gynecology clinics at Bellevue Hospital and at the Ortho Research Foundation. The four remaining cultures were obtained from Dr. Robert A. Hart,\* and from the American Type Culture Collection.

I. Culture No. 9478. Isolated after completion of treatment for trichomonas vaginalis vaginitis. A clinically normal vagina and a Grade I flora by direct smear existed at the time of isolation.

II. Culture P. Obtained from a clinically normal vagina with no history of vaginitis. A Grade I flora was evident by direct smear and culture.

III. Culture R. Isolated following treatment for a trichomonas infection. The vagina was trichomonad free and clinically normal. Upon culture for Döderlein's bacillus, fourteen additional vaginal organisms of different morphology were isolated, although the direct smear indicated a Grade I flora.

IV. Culture W. The patient was in the first trimester of pregnancy. An abundance of Döderlein's bacillus was evident in both the direct smear and culture.

V. Culture H. A clinically normal vagina and a Grade I flora were indicated in the direct smear and by culture.

VI. *Lactobacillus acidophilus* No. 9857. This culture was also listed as "Döderlein's bacillus" and was obtained from the American Type Culture Collection.

VII. *Lactobacillus acidophilus* No. 4357. American Type Culture Collection.

VIII. *Lactobacillus acidophilus*, strain "A." According to Dr. Hart, this strain was isolated from soured milk over twenty years ago.

IX. *Lactobacillus acidophilus*, strain "M." The origin of strain "M" is not known. It was originally obtained from Dr. John Torrey and was sent to us by Dr. Hart.

### Methods

*Development of a Medium.*—The technique employed for obtaining Culture No. 9478 was as follows. A patient was placed in the lithotomy position. The labia were separated manually and a sterile speculum was inserted. Cultures were taken from the posterior fornix with sterile swabs. With the first swab, a direct smear was made by rolling the swab on a sterile slide. The remaining swabs were expressed into beef heart infusion broth (Difeo), acetic acid broth, thioglycollate broth (B.B.L.)† with 10 per cent human serum added, and cysteine-peptone-liver-maltose medium.<sup>14</sup> Dextrose was added in a 1 per cent concentration to each broth medium since Cruickshank<sup>8</sup> established a requirement for a fermentable carbohydrate.

Each of these broth cultures was immediately streaked in duplicate on 1 per cent dextrose agar, dextrose agar with sodium oleate, dextrose blood agar, trypsin digest agar, tomato juice agar,<sup>12</sup> and Weinstein's tomato-milk agar.<sup>13</sup> One set of streaked plates was incubated in a Brewer's anaerobic jar while the other set was incubated under 10 per cent carbon dioxide tension as outlined on page 7 of *Standard Methods*.<sup>15</sup>

With the exception of the thioglycollate serum broth, none of the above broth media provided any gram-positive rods after twenty-four hours' incubation at 37° C. This was possibly due to overgrowth by other vaginal bacteria. The solid media streaked initially from these broth media gave a scant growth of pinpoint colonies, after forty-eight hours' incubation at 37° C. with the exception of trypsin digest agar. This initial streak culture on solid media before incubation of the broth was, therefore, abandoned in subsequent attempts at isolation. The thioglycollate serum broth, which supported a mixed

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culture, including gram-positive rods after incubation, was plated in duplicate on Kulp's tomato juice agar and Weinstein's tomato-milk agar and incubated for forty-eight hours at 37° C. both anaerobically and under 10 per cent carbon dioxide tension.

Although colonies of other organisms were found on both these solid media, it was not difficult to detect pure colonies of gram-positive bacilli in anaerobic culture and under carbon dioxide tension. These colonies of gram-positive organisms were slightly larger on the Weinstein's tomato-milk agar plates. Therefore, the latter medium was selected as the temporary medium for carrying these purified cultures. However, the cultures on this solid medium and in thioglycollate serum broth died off after several weeks of serial culture. Consequently, a search was started for both a broth medium and a solid medium for sustained culture following isolation from thioglycollate serum broth.

On the next attempt, Culture P was successfully isolated from thioglycollate broth. It was found that improved colony growth on the tomato agar media was obtained if the surface was initially flooded with a very thin layer of thioglycollate serum broth.

Culture P was sustained successfully when a substrate combination including all of the ingredients of thioglycollate serum broth and Weinstein's tomato-milk agar was used. The ingredients of these two media are listed in Tables I and II.

TABLE I. WEINSTEIN'S TOMATO-MILK MEDIUM

Filtered tomato juice	200 c.c.
Peptone	5 Gm.
Peptonized milk	10 Gm.
Yeast extract	5 Gm.
Agar	20 Gm.
Distilled water	800 c.c.

TABLE II. THIOGLYCOLLATE SERUM BROTH

Peptone (trypticase, phytone)	20 Gm.
Dextrose	10 Gm.
Sodium chloride	5 Gm.
Dipotassium phosphate	2 Gm.
Sodium thioglycollate	1 Gm.
Methylene blue	0.002 Gm.
Agar	0.5 Gm.
Distilled water	1,000 c.c.
Serum (human)	10 per cent

The total concentration of peptone in the completed B.B.L. thioglycollate broth was 2 per cent. Of this amount, 12.5 per cent is phytone and the remaining peptone is trypticase.

At this point, a variety of media combinations containing the various ingredients of the above combined thioglycollate-tomato juice medium were tried in order to eliminate nonessential components.

Colony size on an agar surface and sustained growth were the criteria for the effectiveness of these media combinations.

In the course of this work it was definitely established that serum and dextrose were required for sustained growth. Therefore, 10 per cent human serum, 1 per cent dextrose, and 1.5 per cent agar were used as a basal medium to which the separate ingredients of the thioglycollate-tomato milk combination were added.

The addition of phytone to the basal medium produced a more prolific growth of colonies. Upon increasing the concentration of phytone, a definite increase in colony size was observed. Optimal growth was obtained with 2 per cent phytone in the final medium. The other ingredients were demonstrated as unimportant and were therefore abandoned.

The formulation of the optimal medium is as follows:

Phytone (B.B.L.)	2 Gm.
Dextrose	1 Gm.
Distilled water	90 c.c.
Serum (human)	10 c.c.

The phytone and dextrose are dissolved and the medium tubed in 9 c.c. amounts. After autoclaving at 15 pounds pressure for fifteen minutes the medium is allowed to cool and 1 c.c. of sterile serum is added to each tube. The serum is adjusted to pH 6 with N/1 HCl and sterilized by filtration. The pH of the final medium varies between 6.1 and 6.5. This medium has been given the name P.D.S. medium (phytone, dextrose, serum). The addition of 1.5 Gm. of agar to the fluid medium before autoclaving provides a solid medium for plate culture.

Broth cultures using P.D.S. medium produced heavy growth of the gram-positive bacillus in twenty-four hours at 37° C. Subsequent isolations of the Döderlein organism from patients with either a Grade I or Grade II flora were readily accomplished with this medium.

The procedure employed was as follows: The vaginal swabs were expressed into P.D.S. broth medium and incubated for twenty-four hours at 37° C. After incubation, the gram-positive rods grew profusely, while the majority of other vaginal organisms present from a Grade II flora were either inhibited or killed by the acidity produced by the rapid growth of Döderlein's bacillus. To isolate the organisms in pure culture, these incubated P.D.S. broth cultures were streaked on the P.D.S. agar medium and incubated anaerobically for forty-eight hours at 37° C. Isolated colonies were picked from the solid medium into P.S.D. broth. Several transfers were carried in the broth medium before being seeded into the following stock culture medium.

The medium devised for maintaining stock cultures was Difco litmus milk medium with 1.5 per cent phytone added. Three hundredths of 1 c.c. of the broth culture was seeded into the litmus milk-phytone medium and incubated for twenty-four hours at 37° C. and then stored in the refrigerator. Transfers were successfully made after three or four weeks storage.

#### Cultural Characteristics and Biochemical Reactions

*Cell Morphology.*—The gram-positive Döderlein organisms vary in length and thickness. They are either straight or curved rods, appearing singly or in short and long chains. The ends may be flat or rounded. All forms change, depending on the age of the culture and the nature of the culture medium.

The photomicrographs show a resemblance between the vaginal bacilli and *Lactobacillus acidophilus*. Cultures P and H which are gram-positive rods occurring singly resemble *L. Acidophilus*, strain "A." Whereas, cultures W, R, and 9857 appear to be morphologically similar to *L. acidophilus*, strain "M."

*Colony Morphology.*—The colony growth of the Döderlein organism on P.D.S. agar medium is punctiform to circular. Isolated colonies are cream colored and opaque with a transparent edge. A large mass of colonies appears

to have a foamy, white surface. The younger colonies are of a soft consistency which, upon aging, become slightly dry and mealy. In the presence of serum, the colonies become surrounded by an aerola of turbid agar.

Anaerobiosis is necessary for initial culturing of this organism, but after several transfers the vaginal bacillus will grow aerobically. However, reduced oxygen tension is recommended for larger colonies and more rapid growth of the adapted strains.

Several strains of *Lactobacillus acidophilus* have been included in this study (see list of cultures studied) for the purpose of determining whether or not *L. acidophilus* colonies can be differentiated from Döderlein's bacillus on the P.D.S. agar medium. Morphologically, it is impossible to distinguish a *Lactobacillus acidophilus* colony from a colony of Döderlein's bacillus.

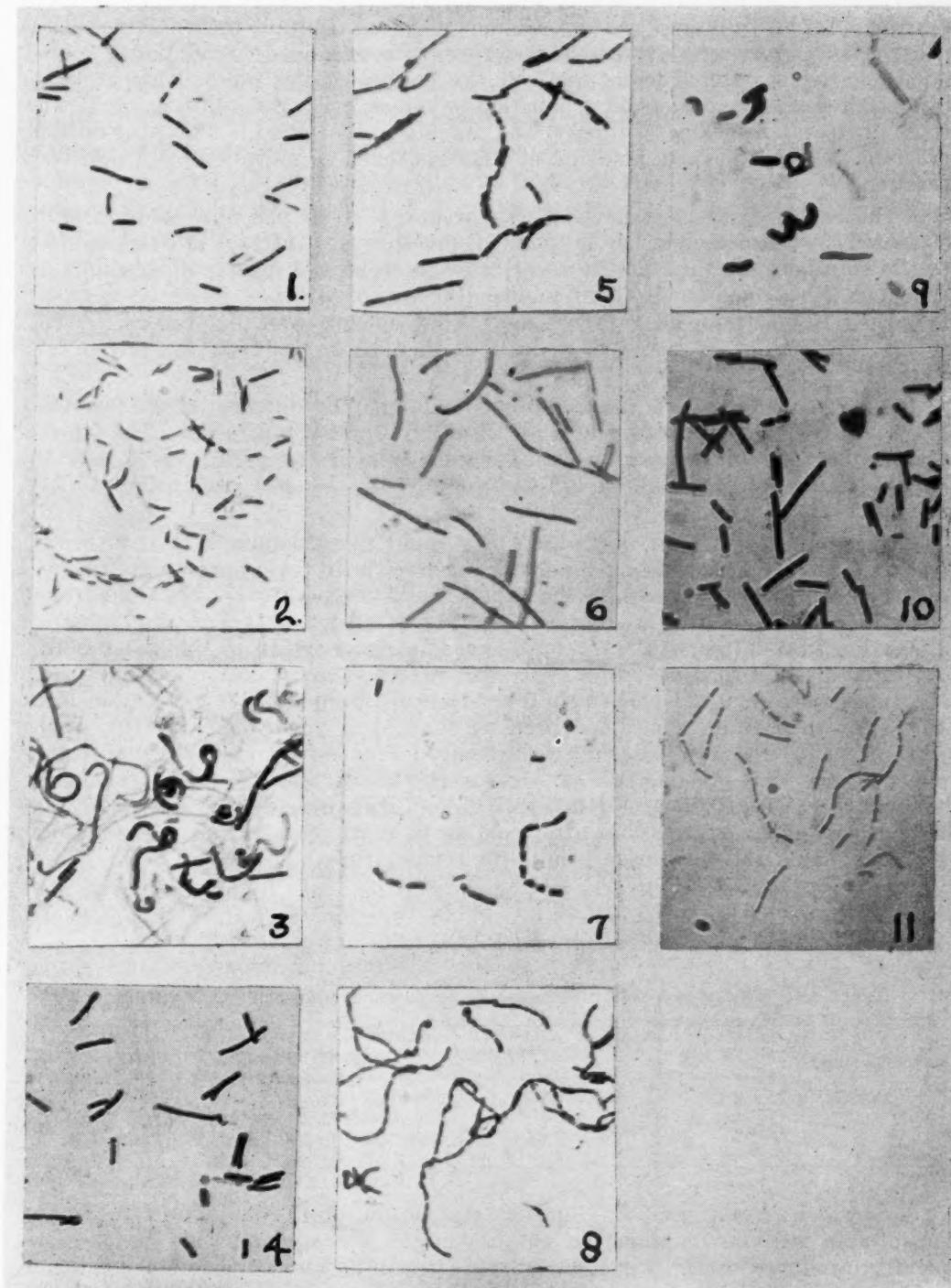
*Broth Cultures.*—The uninoculated P.D.S. broth medium had a clear brownish-red color. With the growth of Döderlein's bacillus or *L. acidophilus*, the medium became very turbid. There was no surface growth produced by either of these cultures, although a heavy, compact, grayish-white sediment developed after 24 hours. Upon aging, heavy growth was noticeable along the sides of the broth tubes. Any odor due to the bacteria was masked by the odor of the phytone.

*Litmus Milk Reactions.*—Cultures of Döderlein's bacillus and *Lactobacillus acidophilus* inoculated into Difco litmus milk gave slow, unreliable reactions. However, with the addition of 1.5 per cent phytone to litmus milk, an acid curd, complete reduction, and peptonization developed in twenty-four to forty-eight hours. The exceptions to this statement were Culture W and *Lactobacillus acidophilus*, strain "A." These two cultures required nine to fourteen days to produce a curd, although an acid reaction and complete reduction occurred in twenty-four to forty-eight hours. These reactions have been found to be consistent and reliable in the presence of phytone.

TABLE III. COMPARISON OF CARBOHYDRATE FERMENTATION REACTIONS

CULTURE R	CULTURE 9857	CULTURE P	CULTURE W	CULTURE H	L. ACID 4357	L. ACID "M"	L. ACID "A"
Sorbitol	-	-	+	+	+	+	+
Raffinose	-	+	-	+	+	+	+
Rhamnose	-	-	-	+	+	+	+
Melezitose	+	+	-	+	+	+	+
Melibiose	+	-	-	+	+	+	+
Galactose	+	+	+	+	+	+	+
Levulose	+	+	+	+	+	+	+
Mannite	-	-	+	+	+	+	+
Maltose	+	+	+	+	+	+	+
Adonitol	-	-	-	+	+	+	+
Cellobiose	+	+	+	+	+	+	+
Glycogen	+	+	+	+	+	+	+
Arabinose	+	+	-	+	+	+	+
Dextrose	+	+	+	+	+	+	+
Trehalose	+	+	+	+	+	+	+
Lactose	+	+	+	+	+	+	+
Glycerine	-	-	-	+	+	+	+
Mannose	+	+	+	+	+	+	+
Sucrose	+	+	+	+	+	+	+
Xylose	-	-	-	+	+	+	+

*Carbohydrate Fermentation Reactions.*—Döderlein's bacillus will not grow well in ordinary culture media, therefore phytone medium without dextrose and with 5 per cent serum was used as a basal medium for fermentation



Comparison of Döderlein's bacillus and related organisms ( $\times 1,200$ ).

Fig. 1.—Culture P, twenty-four hour P.D.S. broth culture; Fig. 2.—Culture P, twenty-four hour P.D.S. agar culture; Fig. 3.—Culture P, one week P.D.S. agar culture; Fig. 4.—Culture P, twenty-four hour thioglycollate-tomato milk agar culture. The following are twenty-four hour P.D.S. broth cultures: Fig. 5.—Döderlein's bacillus No. 9857; Fig. 6.—Culture H; Fig. 7.—Culture W; Fig. 8.—Culture R; Fig. 9.—*L. acidophilus* No. 4357; Fig. 10.—*L. acidophilus* "A"; Fig. 11.—*L. acidophilus* "M."

reactions. This mixture was known in itself to contain fermentable carbohydrates. However, phytone and serum without added carbohydrate permitted only a barely visible growth at the bottom of the tube. This growth did not increase on prolonged incubation, whereas, with the addition of 1 per cent dextrose, a heavy sediment and turbidity occurred. This turbidity, accompanied by a definite lowering of pH, was taken as indicative of a positive reaction.

The carbohydrate to be tested was prepared in 10 per cent solution and sterilized by autoclaving at 15 pounds pressure for fifteen minutes. The sterile solution was then added aseptically to make a 1 per cent solution in the final tubed medium. Three hundredths c.c. of a saline suspension from a washed twenty-four hour P.D.S. agar slant culture was pipetted into each tube. The results of the carbohydrate fermentation reactions are shown in Table III.

As seen in Table III, *L. acidophilus* could not be differentiated from the gram-positive bacilli isolated from Culture W and Culture H. The stock Culture No. 9857 and the gram-positive rods isolated from Cultures R and P gave variable reactions which did not permit any general conclusions to be drawn.

**Thermal Death Point of Culture P.**—Eight c.c. amounts of P.D.S. broth were placed in a constant-temperature water bath for approximately one-half hour to warm the tubes to the experimental temperature. Each tube was then inoculated with 0.03 c.c. of a twenty-four-hour P.D.S. broth culture. Following inoculation, the tubes were immediately returned to the water bath. At intervals of two, three, four, five, ten, fifteen, twenty and thirty minutes, the tubes were removed and subcultures were made by pipetting 0.03 c.c. into P.D.S. broth medium which had been maintained at room temperature. Both sets of tubes, the original cultures removed from the water bath and the subcultures, were incubated for one week at 37° C. The experimental temperatures ranged from 45° to 74° C. For temperature ranges over 56° C., serum was added to the tubes after cooling to room temperature. The results given in Table IV summarize results for temperatures above 66° C.

**Other Biochemical Reactions.**—Such reactions as Indol and hydrogen sulfide formation and the Voges-Proskauer reaction were unreliable, due to masking by the deep red color of the P.D.S. medium.

TABLE IV. THERMAL DEATH POINT FOR TEMPERATURES ABOVE 66° C., CULTURE P.

TEMPERATURE	MINUTES							
	2	3	4	5	10	15	20	30
66° C.	+	+	+	+	+	+	+	+
69° C.	+	+	+	+	+	+	+	+
72° C.	+	+	+	+	+	+	-	-
74° C.	+	+	+	+	+	+	-	-

**Serologic Reactions.**—Phytone-dextrose-serum broth was found to be an unsuitable medium in which to obtain antigen for agglutination tests. The acidity produced by the organism caused a precipitation of the protein material in the medium. Repeated washings did not separate all the protein material from the bacteria. Furthermore, the antigenic properties of the strains under study were found not to remain constant on the P.D.S. solid medium. Therefore, no clear-cut serologic differentiation could be made between the strains of Döderlein's bacillus and the strains of *Lactobacillus acidophilus* through agglutination tests.

### Discussion

Phyton is an enzymatic digest of soy beans, cotton seeds and peanut meal. The pH of various lots received in this laboratory varied between 6.1 to 6.5. Phytone contains a considerable amount of fermentable carbohydrates, including hexose sugars. It has an appreciable sulfur content, including cysteine. Hydrogen sulfide reactions are observed with lead acetate paper when *Eberthella typhosa* is grown in it. Phytone also contains thiamine, riboflavin, nicotinic acid, and pantothenate. The total nitrogen content is approximately 9.8 per cent and ash 6.4 per cent.<sup>16</sup>

The P.D.S. medium is a valuable aid for the isolation and maintenance of Döderlein's bacillus. However, there are indications for a refinement of this medium in order to permit reliable serologic and biochemical differentiations of the various strains encountered.

It is of interest to note that the "complete" chemically defined medium of Sprince and Kupferberg<sup>17</sup> did not sustain growth of these gram-positive bacilli when serum, dextrose, and Wilson's solubilized liver were added to the medium.

### Summary

1. A fluid medium providing optimal growth of Döderlein's bacillus in mass culture has been developed.
2. A solid medium has been devised, using the fluid medium as a substrate.
3. A procedure for successful isolation of Döderlein's bacillus is recorded.
4. The addition of phytone to Bacto litmus milk is recommended for the maintenance of stock cultures.
5. Döderlein's bacillus could not be differentiated from *Lactobacillus acidophilus* through carbohydrate fermentation and litmus milk reactions.
6. The thermal death point for one culture is recorded as 72° C. for twenty minutes in the absence of blood serum.
7. Biochemical and serologic differentiations cannot be made until the culture medium is further refined.

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## A COMPARATIVE STUDY OF THE EFFICACY OF CERTAIN DRUGS IN PROMOTING EVACUATION OF THE FEMALE BLADDER FOLLOWING GYNECOLOGIC OPERATIONS\*

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**A** NUMBER of studies have been carried out in recent years involving the problem of urinary retention after operation. Therapeutic agents have been made available from time to time with physiologic properties ascribed to them that seem difficult to reproduce clinically. Instillation of mercurochrome solution into the bladder at the time of operation has achieved more prominence than any other agent.

On the ward service of the Division of Gynecology, Department of Obstetrics and Gynecology at the Jefferson Medical College Hospital, when suggestive measures failed to promote spontaneous bladder evacuation, a "bladder laxative" was formerly employed. This consisted instilling 30 c.c. of sterile glycerin into the distended bladder by catheter, and then withdrawing the catheter immediately. This procedure was successful with a certain number of patients, but the method has more or less fallen into disuse in recent years, although it is still employed occasionally.

The present study was undertaken in an effort to determine the efficacy of various types of medication designed to decrease the number of catheterizations following gynecologic operations.

Catheterization after operation or the introduction of an indwelling catheter has definite disadvantages, and any type of therapy that will reduce the incidence of catheterization or preclude the use of the indwelling catheter is certainly desirable.

The array of therapeutic agents used in this connection further emphasizes the fact that none of the agents in use is always entirely satisfactory.

The investigation carried out comprises a comparative study of five series of patients, one a control, and four series in which different medicaments and methods were used, as follows:

1. One hundred in whom no medication was employed.
2. One hundred in whom mercurochrome was instilled into the bladder at the time of operation.
3. One hundred in whom acriflavine was instilled into the bladder at the time of operation.
4. One hundred in whom prostigmine methyl sulfate was injected hypodermically prior to operation and also after operation.
5. Twenty-two in whom "Doryl" was injected hypodermically after operation.

\*Read at a meeting of the Philadelphia Obstetrical Society, Dec. 4, 1947.

In addition to these serial studies, cystometric studies were performed on a group of supposedly normal women (nonoperative cases) before and after the use of instillations of mercurochrome, acriflavine, and prostigmine methyl sulfate by injection.

### Control Series

The first group of patients studied were those in whom we did not employ any type of medication in an attempt to induce micturition, other than the suggestive measures usually employed in trying to aid the patient to void. Seventy-seven per cent of this series were catheterized.

TABLE I. CONTROL SERIES

TYPE OF OPERATION	NUMBER OF PATIENTS	NUMBER OF CATHETERIZED	PER CENT CATHETERIZED
Abdominal section	44	27	61.3
Plastics	30	27	90.0
Plastic and abdominal sections	26	23	88.4
Total	100	77	77.0

In analyzing this series we find that 61.3 per cent of those having sections were catheterized at least once, while 90.0 per cent of the plastic cases and 88.4 per cent of those having a plastic and section were catheterized. (Table I.)

### Mercurochrome Series

The second group studied were those in whom mercurochrome was used. Fifteen cubic centimeters of a 0.5 per cent solution of mercurochrome were instilled into the patient's bladder after catheterization at the time of operation.

TABLE II. MERCUROCHROME SERIES

TYPE OF OPERATION	NUMBER OF PATIENTS	NUMBER CATHETERIZED	PER CENT CATHETERIZED
Abdominal section	56	14	25.0
Plastic	34	16	47.1
Plastic and abdominal section	10	7	70.0
Total	100	37	37.0

The highest percentage of catheterizations (70 per cent) was among those having plastic and sections. Of the plastic procedures alone catheterization was necessary in 47.1 per cent, while only 25 per cent having abdominal sections were catheterized. Thirty seven per cent of the entire series in this group were catheterized. Two patients in this series developed hematuria, and several complained of unusual tenesmus (Table II).

### Acriflavine Series

In the third series, 15 e.c. of a 1 to 2,000 solution of acriflavine were instilled into the bladder prior to operation, although a 1 to 1,000 solution was first used for awhile.

Eighty-three and three-tenths per cent of those having a plastic and section were catheterized, and 72.7 per cent of those having plastic procedures only were catheterized, and 53 per cent of those having abdominal section alone

were catheterized. Acriflavine (1 to 1,000) was used initially in a small group of the patients in this series, but this seemed to cause a rather marked degree of bladder irritability, frequency, and tenesmus. Using a 1 to 2,000 solution later on, we had less trouble, although a certain number still developed frequency and tenesmus. Sixty-one patients of the one hundred patients in this series were catheterized in this group (Table III).

TABLE III. ACRIFLAVINE SERIES

TYPE OF OPERATION	NUMBER OF PATIENTS	NUMBER CATHETERIZED	PER CENT CATHETERIZED
Abdominal section	66	35	53.0
Plastic	22	16	72.7
Plastic and abdominal section	12	10	83.3
Total	100	61	61.0

#### Prostigmine Methyl Sulfate Series

In the fourth series 1 c.c. of a 1 to 1000 solution of prostigmine methyl sulfate was injected hypodermically twelve, six, and three hours prior to operation; 1 c.c. was also injected six, nine, fifteen, and twenty-one hours after operation.

In subdividing these cases we find that 58.6 per cent of the patients having abdominal sections were catheterized at least once, while 100 per cent of those having plastic procedure and 66.6 per cent of those having a plastic and section were catheterized.

TABLE IV. PROSTIGMINE METHYL SULFATE SERIES

TYPE OF OPERATION	NUMBER OF PATIENTS	NUMBER CATHETERIZED	PER CENT CATHETERIZED
Abdominal section	75	44	58.6
Plastic	13	13	100.0
Plastic and abdominal section	12	8	66.6
Total	100	65	65.0

Sixty-five per cent of the hundred patients in this series were catheterized (Table IV).

#### "Doryl" Series

In the final series of patients studied, 1 c.c. Doryl was used postoperatively by hypodermic injection, upon patients who could not void voluntarily.

While no untoward reactions were observed in any of the patients in this series, we were aware of some patients who had previously had reactions to the drug, and therefore were not comfortable about its use. The drug was used in 22 patients who could not void, and it was successful in twelve (54.5 per cent). We do not feel that the results were sufficiently impressive to warrant continued use of the drug in a larger number of patients.

Reference to the composite Table V would indicate that mercurochrome was the most effective type of medication used. While only 37.0 per cent of the total number were catheterized, 70.0 per cent of those having a plastic and abdominal section required catheterization. Mercurochrome did not seem to be as effective in our series as in Woodruff and Te Linde's, however.

TABLE V. COMPOSITE CHART—FOUR SERIES

	ABDOMINAL SECTION	PLASTIC	PLASTIC AND ABDOMINAL SECTION	TOTAL PER CENT CATHETERIZED
Control series	61.3 per cent	90.0 per cent	88.4 per cent	77.0 per cent
Mercurochrome series	25.0 per cent	47.1 per cent	70.0 per cent	37.0 per cent
Aeriflavine series	53.0 per cent	72.7 per cent	83.3 per cent	61.0 per cent
Prostigmine methyl sulfate series	58.6 per cent	100.0 per cent	66.6 per cent	65.0 per cent

Patients requiring plastic and section as a whole required more catheterizations than did those having either plastic operations or abdominal sections, while in the abdominal sections alone fewer catheterizations were required than in plastic operations alone.

The series in which prostigmine methyl sulfate was used required the highest percentage of catheterizations in the total series, and there were no complaints or untoward local or general reactions afterward.

Aeriflavine proved to be too irritating to the bladder mucosa to recommend its use. If used in stronger concentration than 1 to 2,000 it was uncomfortable. Too great an inference cannot be drawn from the groups having a plastic and section, since in each of these there was a relatively small number of patients; hence no definite conclusions should be drawn until a larger number of patients have been evaluated.

#### Discussion of Mode of Action

It is thought that the mode of action in the use of mercurochrome and also with aeriflavine is through an irritative action upon the mucous membrane of the bladder; prostigmine methyl sulfate, however, acts by stimulating the parasympathetic nerves which cause the detrusor musculature to contract and the sphincter fibers to relax. Regardless of specific physiologic action, it would seem that an increase in bladder tonicity would be reflected in an observation of cystic pressure, and with this in mind cystometric studies were carried out on some patients with apparently normal bladders, both before and after the employment of the medicinal agents previously mentioned. These results were somewhat surprising, for they did not coincide with our clinical experience.

In five cystometric examinations made on such patients before and after the instillation of mercurochrome (15 c.c. of 0.5 per cent solution) there was practically no change observed in the intracystic pressure after the instillation of mercurochrome, from that noted beforehand.

Using aeriflavine (1 to 2,000 solution) proved results similar to those noted with mercurochrome.

We were surprised, however, in the use of prostigmine methyl sulfate (1 to 4,000 solution) given hypodermically one hour and two hours prior to the test, for in this instance constant, but not marked rise in intracystic pressure was noted.

These tests were made with a simple water manometer, and the recordings were expressed in centimeters of water and the findings for the normal intracystic pressure were similar to those reported by McLellan, namely, 1 to 8-15 cm. of water.

The causative factor in the postoperative retention of urine in gynecologic patients has been attributed grossly to trauma of the adjacent tissues. This is undoubtedly true to some extent, even though patients with other than pelvic operations frequently have retention of urine. Nevertheless, it is generally

acknowledged that the physiology of micturition has been interfered with, and perhaps various factors are involved at different times. Additional etiologic factors frequently mentioned are: length of operation, type of operation, type of anesthesia, psyche of patients, position of patient while attempting to void, postoperative medication, diminished sensibility of bladder mucosa, vegetative unbalance, lack of parasympathetic and overaction of sympathetic nerves.

Jordan carried out cystometric studies on dogs using pilocarpine, pituitrin, potassium citrate and atropine, all of which gave a marked increase in tonus except atropine. Pilocarpine was used in the human being in smaller dosage but only slight rise in pressure resulted; larger doses caused abdominal pain and profuse perspiration. Acetylcholine caused only slight rise in pressure, while potassium acetate given orally in a dilution of 1 to 15 caused a definite rise in bladder tonus. Cystometric studies were also performed by Gernon, Palmer, and McKenna using mecholyl and gynergyn. Both of these drugs caused increased intracystic pressure in a different manner. The effect of mecholyl is obtained by causing a parasympathetic preponderance, while gynergyn also causes parasympathetic predominance by inhibition of both the motor and inhibitory sympathetic endings.

Since retention of urine is noted in patients other than those having gynecologic operations, it would undoubtedly seem that several factors enter into the picture, rather than one. On the other hand since retention occurs so much more frequently after gynecologic operations, tissue trauma is probably the most important single factor. Operative procedures of any type, either on the vulva, the anterior or posterior vaginal walls, urethra, or cervix are more likely to cause retention than abdominal section alone.

In the course of abdominal section the parasympathetic nerves passing over the brim of the pelvis can easily be traumatized because of the prominence of the sacrum and the proximity of the presacral plexus. Pressure in this area by the operator's hand and also by packs can be sufficient to alter the physiology of these nerves.

### Conclusions

1. Five series of patients, one a control series, were studied in order to determine the effect of therapeutic agents in overcoming postoperative bladder retention.
2. Instillation of mercurochrome, 15 c.c. of a 0.5 per cent solution, into the bladder at the time of operation was found to be most effective.
3. Cystometrically there was little, if any, change in the intracystic pressure before and after the use of mercurochrome and aeriflavine, however, there was a slight rise in the case of the prostigmine.

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### Discussion

DR. ROBERT A. KIMBROUGH.—The evaluation of any form of therapy for conditions which tend to right themselves spontaneously is indeed a difficult, if not an impossible matter. The need for catheterization "at least once" constitutes Dr. Lintgen's criterion

of inadequate bladder function in this study. It would be interesting to have a further breakdown as to the number of catheterizations required in each group and the length of time over which catheterization was necessary. From his studies it would appear that the use of 15 c.c. of  $\frac{1}{2}$  per cent solution of mercurochrome is superior to the other methods which he has utilized. In our hands instillation of any solution proved so disappointing that for the past several years we have utilized an indwelling catheter for twenty-four hours in simple cases, and for forty-eight hours in extensive plastic operations and in cases of total hysterectomy. It is my belief that the bladder, postoperatively, causes little concern except in those cases which have been subjected to a repair of the anterior vaginal wall. The slow return of normal bladder function is probably due to relatively poor hemostasis in anterior colporrhaphy. The bleeding usually comes from the sulcus underneath the descending pubic ramus where it is almost impossible to ligate every small vein. A small organized hematoma beneath the bladder neck probably interferes considerably with sphincteric function. It is suggested, therefore, we attempt to secure as near absolute hemostasis as possible before closure of the anterior vaginal wall.

When Dr. Lintgen closes the discussion I would like to know more about "Doryl," particularly the rationale of its use. I would like also to know what his experience has been with tidal drainage of the bladder which does not begin to function within a few days. On several occasions we have found the results of this method most gratifying. And, was there any less tendency toward retention after patients started to void, with one preparation or another?

DR. MARY D. PETTIT.—I would like to ask if there has been any difference in the ambulation time operative during the study. Dr. Scheffey brought out this point and we also have found our recent tendency to earlier ambulation has reduced the number of catheterizations markedly. I would like to say that at the beginning of the war period at the Albany Hospital mercurochrome was used routinely postoperatively in bladders. During the latter part of the war period I was not there and I do not know the exact statistical reasons why they stopped using it. I do know that there was much tenesmus and hematuria and those were two reasons for the discontinuance of the procedure as a routine.

DR. LEWIS C. SCHEFFEY.—Dr. Lintgen has shown great interest in this subject which he has pursued assiduously for many years by studying the behavior of the bladder both with respect to postoperative infection and to voluntary urination after gynecologic operations. I know that his persistent and meticulous study in these patients has been demonstrated in the careful tables that he has presented. It would seem from this study, as Dr. Kimbrough has said, that mercurochrome was the most effective of the agents used. That brings up the question as to how often and how consistently continuous drainage should be employed following gynecologic operations. Over a period of years one acquires certain beliefs, or rather certain peculiarities of action. One of the things that has found favor with me has been continuous drainage with intermittent irrigation ("Y" set), rather than with an indwelling catheter alone, although we now have the improved Foley catheter which is more suitable than the mushroom catheter for this purpose. When the nursing problem is difficult, continuous drainage for several days may be the better plan. However, when we have operated to correct cases of incontinence, and when a patient has not been able to hold her urine, continuous drainage may cause a certain amount of paresis of the bladder and urethra and we may thus contribute to the defeat of our procedure. My own practice, after operating upon patients with distressing incontinence by the plication method, is to have been relieved by single catheterizations, for there is an excellent psychological effect upon a woman who has been losing her urine for several years when she finds that she cannot urinate at all by herself.

DR. SCHEFFEY.—I wonder whether the increasing tendency toward early ambulation will not further voluntary voiding in these cases, although I do not like to allow a patient out of bed in two or three days after an extensive plastic procedure. I think that we are

indebted to Dr. Lintgen for bringing this recent work of his to our attention as a corollary to his work in the past, and we have profited by the presentation and discussion.

DR. LINTGEN (Closing).—To answer Dr. Kimbrough's question about "Doryl." We did not have any adverse reactions, but we discontinued its use because of the unfavorable newspaper publicity about cases in which Doryl was used intravenously and several patients died. We discontinued using it at that time, and we have not used it since. Tidal drainage we do use and like it very much. Regarding Dr. Fetterman's question on early ambulation: this study was done prior to the time early ambulation was initiated, but I feel sure early ambulation will make patients void much more quickly after operation. These studies indicate that none of the drugs are too good, and as a result most of us at Jefferson Hospital use an indwelling catheter, especially for plastic cases, and practically in all of the sections. Some of us still use mercurochrome, but have abandoned the use of the other drugs.

## SIMULTANEOUS INTRAUTERINE AND EXTRAUTERINE PREGNANCY

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**S**IMULTANEOUS ectopic and intrauterine pregnancy is a comparatively uncommon condition of more than usual interest. The condition is sufficiently engaging to have arrested the attention of a few authors and to have been the subject of some excellent reviews. The purpose of this paper is to review clinically the cases which have been reported since 1935, to arrive at the approximate total number of cases which are known to date, since many of the earlier case reports are incomplete, and to report the cases which have been seen at the Mayo Clinic.

### Incidence

The total number of cases reported through 1938 was 353, according to Ludwig.<sup>1</sup> This total was decided upon by him through a study of previous compilations of Gemmell and Murray,<sup>2</sup> Mathieu,<sup>3</sup> Novak,<sup>4</sup> and Bland and associates,<sup>5</sup> and by adding seventeen cases which he found reported in the literature, plus three of his own. Since 1938, other authors<sup>6, 7</sup> have studied the literature and discovered several cases which were previously not included in the totals. Mitra,<sup>6</sup> in 1940, reported on seventeen cases and Sloat and Peterson,<sup>7</sup> in 1938, reported on sixteen, including their own; however, since it was found that some of these had been reported on by other writers also, Mitra actually added four new cases, including his own, and Sloat and Peterson added eight new cases, thus giving a total of 365. We were able to find thirty-one cases, including our own, which had not been included in previous compilations.<sup>8-34</sup> The sum total of cases to date, therefore, seems to be 396, including Ludwig's 353, Mitra's four, Sloat and Peterson's eight and our thirty-one. However, from this grand total of cases we feel that at least one case should be subtracted, for reference to the original work cited showed that the condition was not present (Marta<sup>35</sup>); therefore, the total number of cases is probably 395.

The term "simultaneous intrauterine and extrauterine" pregnancy as used herein refers to impregnation of the ectopic and uterine ova within a short time of each other. Faxon<sup>36</sup> expressed the belief that, of approximately 250 cases, 10 per cent represented an intrauterine pregnancy superimposed upon an ectopic pregnancy that had occurred one month to several years previously. The majority of these cases represented twin pregnancy with one ovum implanting ectopically and the other entopically.<sup>11</sup> The incidence of twins has been given as about 1.12 per cent of all births and fraternal-twin pregnancy occurs in about 75 per cent of cases of twins. Thus, the expected incidence of fraternal-twin pregnancy would be approximately 0.8 per cent of all pregnancies, and we can infer, then, that the expected incidence of simultaneous intrauterine and extrauterine pregnancy, calculated on this basis, would be about 0.8 per cent of all ectopic pregnancies, or 1 in 125. Martin and Meyer<sup>37</sup> gave the incidence one in 105. Furthermore, if the incidence of ectopic pregnancy is 0.37 per cent of all pregnancies and the incidence of simultaneous intrauterine and extrauterine pregnancy is 0.8 per cent of all ectopic pregnancies, then 0.37 per cent multiplied by 0.8 per cent gives a value of about

0.003 per cent, which would represent the approximate incidence of simultaneous intrauterine and extrauterine pregnancy in all pregnancies. The incidence at the Mayo Clinic has been two cases in 13,527 deliveries, or 0.015 per cent.

#### Review of Case Reports in the Literature Since 1935

For the purpose of review for this paper, we studied the case reports which have appeared in the literature from Jan. 1, 1935, through February, 1947. During this time, seventy cases have been reported,<sup>1, 3, 6-62</sup> including the two we are reporting herewith. One of the seventy cases was that of a lithopedion which the patient carried for twenty-six years,<sup>3</sup> leaving sixty-nine cases of simultaneous intrauterine and extrauterine pregnancy which we studied, including the two we are reporting. Among these cases, there were some noteworthy facts. One of the pregnancies occurred in the ovary<sup>29</sup> and one was an interstitial ectopic pregnancy for which a hysterectomy was performed.<sup>53</sup> In two cases, the authors noted the existence of two corpora lutea of pregnancy,<sup>26, 53</sup> indicating that, in these patients, there was a possibility of coexistent pregnancies. In sixty-two recorded instances, the right Fallopian tube was involved twenty-nine times, and the left Fallopian tube, thirty-three times. At the time of operation, the uterus was noted to be enlarged in thirty-seven patients; silence on the part of the surgeon does not mean that the uterus was not enlarged, for the uterus normally enlarges in the presence of an ectopic pregnancy. One patient had a mummified seven months' fetus which was obstructing the birth passage during labor. This was found when cesarean section was performed to deliver the live twin.<sup>48</sup>

In the past, this condition has been considered to occur in the older age group.<sup>11</sup> Generally, we found this to be true. Of the sixty-nine patients included in our study, twelve (17.4 per cent) were under twenty-six years of age, twenty-one (30.4 per cent) were twenty-six to thirty years of age, seventeen (24.6 per cent) were thirty-one to thirty-five years of age, fourteen (20.3 per cent) were thirty-six to forty years of age, one was over forty years of age and the age of four patients (5.8 per cent) was unknown. Fifty-three patients (76.8 per cent) were twenty-six years of age or over.

The maternal mortality rate has been considered high. In 1940, the mortality rate for cases up to that time was 19 per cent.<sup>11</sup> In the group of cases we studied, which were reported from 1935 to the present, there was a report of one maternal death in sixty-nine cases, a rate of 1.4 per cent.

Heterotopic pregnancy occurs with greater frequency in the multipara than in the woman who has not had children. In our series, forty-eight patients (70 per cent) were multiparas, ten (14 per cent) were primiparas and in eleven cases (16 per cent) the parity was not known.

In fifty-four cases, the average duration of extrauterine pregnancy was estimated to be 7.7 weeks. Six cases were not included in this estimation because the pregnancy had continued so far beyond the first trimester that their inclusion would have overbalanced the estimate, and, in nine other cases, the duration of the ectopic pregnancy could not be estimated.

Of the six cases which were not included in the estimation of average duration of pregnancy, in four, the ectopic pregnancy reached term. In these four cases, two of the infants lived,<sup>21, 42</sup> one died in the abdomen<sup>14</sup> and one died after transabdominal delivery.<sup>25</sup> The fifth patient was operated on at seven and a half months' gestation and both fetuses died.<sup>31</sup> The sixth patient was delivered of a live baby by cesarean section when the birth canal was found to be obstructed by a mummified seven months' ectopic fetus.<sup>48</sup> Of the

six corresponding intrauterine pregnancies, in three the patient went to term,<sup>21, 25, 42</sup> in the fourth the patient aborted in the first trimester<sup>14</sup>; in the fifth, the patient had an ectopic pregnancy and was operated on at seven and a half months' gestation and the twin fetuses died.<sup>31</sup> The sixth patient was delivered of the intrauterine fetus by cesarean section when the birth canal was found to be obstructed by a seven months' mummified ectopic fetus.<sup>48</sup>

The time elapsing from the last menstrual period to the onset of symptoms for which an operation was done varied from four to eighteen weeks in forty-eight patients, with an average of 8.7 weeks.

The rate of survival of the intrauterine fetuses was very satisfactory. In twenty-nine patients, the fetus in the uterus reached a viable age.<sup>1, 10, 11, 16-19, 21-25, 27-31, 33, 36, 39, 40, 42, 48, 49, 51, 55, 56</sup> On the other hand, twenty-nine patients did not retain the intrauterine fetus;<sup>1, 3, 6, 7, 9, 11-14, 20, 26, 32, 34, 37, 38, 41, 44-47, 50, 52-54, 56, 58, 61, 62</sup> however, in fourteen of these, the intrauterine pregnancy was disturbed before discovery of the ectopic pregnancy, either by spontaneous abortion, curettage, hysterectomy, or injury, as occurred in one case in which the fetus was killed when the mother was kicked by a horse<sup>1, 3, 7, 11-13, 21, 34, 45, 47, 52, 58</sup>; the other fifteen patients lost the intrauterine fetus after discovery of the ectopic pregnancy. In eleven cases, the outcome of the intrauterine pregnancy could not be determined. The possible fetal survival rate after termination of the ectopic pregnancy was, therefore, twenty-nine out of forty-four (65.9 per cent).

The preoperative diagnosis was correctly made six times in sixty-nine cases.<sup>1, 11, 21, 32, 62</sup> In these six cases, however, two patients first had had spontaneous abortions<sup>1, 11</sup>, and, in one, fetal death from external trauma occurred before the ectopic pregnancy was diagnosed.<sup>21</sup> Correct preoperative diagnosis, therefore, occurred three times in sixty-nine cases (4.3 per cent). Even after the abdomen was opened, in sixty-three cases, the diagnosis of coexistent intrauterine pregnancy was made and recorded in only twenty cases.<sup>1, 6, 10, 11, 16, 20, 21, 29, 31, 36, 37, 39, 41, 44, 46, 48, 50, 53, 62</sup> The relatively low incidence of accurate operative diagnosis is perhaps explained both by the infrequent occurrence of this condition and by the fact that enlargement of the uterus frequently occurs during an ectopic pregnancy. When ectopic pregnancy is found the surgeon is not likely to think of a coexisting intrauterine pregnancy.

As indicated above, six patients did not have sufficient symptoms for surgical exploration and, of these six, in four the ectopic fetuses reached term, in one it reached seven and one-half months' gestation, and in one a mummified ectopic fetus was found at seven months' gestation.

#### Report of Cases

CASE 1.—A 29-year-old white woman was admitted to the hospital complaining of generalized abdominal pain which had begun two weeks prior to admission. Three weeks before admission, at the time when a menstrual flow should have occurred, the patient had abdominal cramps and backache which lasted for three days and then ceased. No menstrual flow developed. During the succeeding week the patient had no complaints; then, two weeks before admission, low bilateral abdominal pain, which was worse on the left side, developed. The pain continued to become progressively more severe, and, at the time of admission, she had generalized abdominal pain. The patient had vomited from one to three times daily for two days. The last bowel movement had occurred two days prior to admission and the stool was black, but the patient had been taking some medicine for "gas," which she had passed freely until two days before being seen.

The patient had been treated for Neisserian infection in 1937. She had had two living children, followed by three spontaneous abortions which occurred at about three months' gestation. The last regular menstrual period was two and one-half months prior to admission.

The blood pressure was 94 systolic and 64 diastolic, expressed in millimeters of mercury. A systolic murmur was heard over the entire precordium. Numerous râles were heard at the base of the left lung and vocal fremitus was decreased. The abdomen was distended and no peristaltic sounds could be heard. The upper part of the abdomen was slightly tender, the lower part was very tender bilaterally and the muscles were rigid. There was marked rebound tenderness of the lower part of the abdominal wall. Pelvic examination revealed that the cervix was large and softened. The uterus could not be outlined because of pain. Pain was elicited by moving the cervix and there was tenderness in both fornices.

A catheterized specimen of urine was taken. The specific gravity was 1.021 and the reaction was alkaline. There were occasional erythrocytes and leucocytes. The hemoglobin concentration was 11.6 Gm. per 100 c.c. of blood and the leucocyte count was 11,100 per c.mm. of blood. The differential leucocyte distribution was lymphocytes 18 per cent, monocytes 4 per cent, neutrophils 77 per cent and eosinophils 1 per cent. The sedimentation rate was 63 mm. in one hour. Cultures of material taken from the cervical and urethral ostia were negative for Neisserian organisms.

It was decided that the patient had an acute abdominal condition requiring surgical exploration, possibly a degenerating fibroid, and forty-eight hours from the time of admission she was operated on.

With the patient under nitrous oxide and ether anesthesia, a primary midline incision was made in the abdomen. Approximately 150 c.c. of blood in the abdomen had escaped from the fimbriated end of the left Fallopian tube. This tube was the site of an unruptured ectopic pregnancy. The condition of the ovaries and the size of the uterus were not noted. Bilateral salpingectomy was done at the patient's request. Uterine retroversion and prolapse were corrected by a Gilliam type of suspension.

The pathologist's finding was chronic salpingitis in the right Fallopian tube and ectopic pregnancy in the left.

The patient was dismissed from the hospital on the tenth postoperative day. Five days later, at the time of dismissal from the clinic, the cervix was still soft and the uterus was anteverted.

Three months later the patient registered at the prenatal clinic. The size of the uterus was that of a four months' gestation. The result of a Friedman test was reported as positive. After an uneventful prenatal course, the patient delivered spontaneously a full-term male child.

CASE 2.—A 34-year-old white woman was first seen at her home on June 5, 1946, because of pain in the right lower quadrant. The pain had begun five days before she asked for help. It was mild at first but became severe and cramping. The patient had what was described as a scant menstruation for two days, which accompanied the pain. During the day on which she was seen, she had experienced severe right lower quadrant pain which extended down her thigh and forced her to stop working. The next day she was admitted to the hospital after having spent a quiet night, but before admission the same pain had recurred.

The patient stated that her menstrual periods had always been regular, but that she had had none for two months before admission to the hospital. She was gravida i, para 0. She had had pulmonary tuberculosis and her appendix had been removed eight years prior to admission.

The blood pressure was 125 systolic and 75 diastolic. The pulse rate was 96 per minute, and the temperature was 99.8° F. Pelvic examination revealed oozing of blood from the external cervical os and tenderness when the cervix was lifted. The adnexal regions were somewhat tender.

The specific gravity of the urine was 1.020 and the reaction was acid. There was grade 1 albuminuria (on the basis of 1 to 4 in which 1 represents the least and 4 the most severe condition) and a slight amount of reducing substances was present in the urine. The concentration of hemoglobin was 10.6 Gm. per 100 c.c. of blood and the leucocyte count was 8,600 per c.mm. Cultures taken from the cervix and urethra were negative for *Neisseria gonorrhoeae*. The result of the Friedman test was reported as positive.

Over a period of five days, the patient continued to have mild, cramping, abdominal pain with some spotting of blood. She then experienced some pain in the region of the right shoulder and in the right adnexal region when examined bimanually. It was thought, after examination with the patient under anesthesia, that ectopic pregnancy existed on the right side, although no definite mass but only some thickening in the right adnexal region was noted.

At abdominal exploration, the lumen of the right Fallopian tube, at its middle portion, was found to be the site of an unruptured ectopic pregnancy and the tube was removed. About 100 c.c. of old, clotted blood was present in the pelvic cavity. The uterus was enlarged to a size consistent with that at two and one-half months' pregnancy and it was believed to be the site of another pregnancy.

One month later the patient was admitted to the prenatal clinic and an intrauterine pregnancy of three months' duration was present. After an uneventful prenatal course and after a labor in which the first stage lasted thirty-one hours and the second stage one hour, the patient was delivered of a full-term, living, female infant.

### Discussion

The most significant point we encountered in our study of simultaneous intrauterine and extrauterine pregnancy was the drop in the maternal fatality rate from an over-all figure of 19 per cent to one of 1.4 per cent, which is compatible with a more modern concept of surgical risk. The lower rate is, of course, due to earlier diagnosis of the ectopic condition, earlier operation, and replacement of the blood and fluid loss. The replacement of blood promptly is the largest single recent factor in the reduction of fatality rates since everyone has agreed for years that the only treatment for ectopic pregnancies is early operation.

There was but one maternal death in the series since 1935, and, for this reason, we felt that the added complication of an intrauterine pregnancy did not appreciably increase the surgical risk. This death occurred after a two-day labor and cesarean section, at which a mummified fetus was found obstructing the birth canal. Death was attributed to a combination of maternal exhaustion, blood loss, and peritonitis.

The survival rate of the intrauterine fetuses is also of interest. Twenty-nine living children were delivered from the sixty-eight surviving patients. Since the outcome of the pregnancy is not mentioned in eleven cases and since, in fourteen, the intrauterine pregnancy was terminated before or at operation, the occurrence of twenty-nine live births out of a possible forty-three is remarkable.

The diagnosis was correctly made preoperatively six times in the group of sixty-nine cases, but in three, abortion of the intrauterine fetus before operation made the diagnosis easier. The diagnosis depends, of course, on evidence for an intrauterine, as well as an extrauterine, pregnancy. If a patient gives a history of a previous ectopic pregnancy, it is an added point for the possibility of a second one; chiefly, however, the history reveals the possibility of conception, as evidenced by a period of amenorrhea lasting a few days to several weeks, followed by a period of irregular spotting. If the spotting is due to an ectopic pregnancy the blood is often dark and viscous,

while the bleeding from an aborting intrauterine pregnancy is usually heavier and the blood is a brighter red. If there is an excess of vaginal bleeding plus signs of peritoneal irritation, a simultaneous intrauterine and extrauterine pregnancy can at least be suspected.

The indefinite signs of early pregnancy are most often conspicuous by their absence. Morning nausea, tingling of the breasts, increased pigmentation and cyanosis of the vaginal mucosa are helpful, if present. The cervix softens early and this sign is suggestive of pregnancy. Enlargement of the uterus occurs with either an ectopic or an intrauterine pregnancy and, if the enlargement is marked, then the possibility of coexisting intrauterine pregnancy should be suspected.

The presence of pelvic pain is very helpful. Such pain generally begins when internal bleeding starts. The overwhelming pain, with collapse, shock and so forth, of the complete rupture of a tube with massive intra-abdominal hemorrhage is not being stressed, as in these cases, the evidence that an intra-abdominal calamity has occurred is so apparent that the diagnosis should be made at once. The cases in which the condition starts as just a little intra-abdominal bleeding, the types of tubal abortion in which the products of conception are loosened but still in the tube, are the ones in which the possibility of diagnosis is offered before a catastrophe occurs. In this group, the pain is usually in one side or the other and is colicky at the beginning. This is followed by a dull, aching type of pain as a small amount of blood begins to collect in the peritoneal cavity. This blood, gravitating into the cul-de-sac, often causes painful defecation, which is a most helpful symptom.

The physical findings of a tender mass in one fornix and possibly a fullness and tenderness in the cul-de-sac are indicative of ectopic pregnancy.

However, even at operation, the diagnosis of simultaneous intrauterine and extrauterine pregnancy is not easy and in only twenty patients was it made by the surgeon. The enlargement that the uterus undergoes with ectopic pregnancy is sufficiently great that, unless the enlargement is marked, the surgeon closes the abdomen without suspecting the presence of the coexisting intrauterine fetus. A second sign that is excellent for double pregnancies, when it occurs, is the presence of two corpora lutea in the ovaries, indicating the possibility of two conceptions.

The treatment of these patients is that of any patient with an ectopic pregnancy, namely, early exploration. If an intrauterine pregnancy is also found, the patient can be given very definite hope of bearing a living child.

#### Summary and Conclusions

According to our study, the number of reported cases of simultaneous ectopic and intrauterine pregnancy, including our own, is approximately 395.

The maternal fatality rate in the cases encountered in the last eleven years compares favorably with that in cases of single ectopic pregnancy and, therefore, the added complication of the intrauterine pregnancy does not seem to increase the risk to the mother.

Of the sixty-nine patients referred to in the reports made in the last eleven years, twenty-nine were known to have delivered living children and only fifteen were known to have experienced termination of the intrauterine pregnancy after surgical treatment for the ectopic pregnancy.

Although we cannot often expect to make the diagnosis of double pregnancy in early cases, we should certainly be able, it seems, to make the diagnosis at the time of operation in more than twenty out of sixty-three cases.

In our two cases reported herein, the patients were delivered of normal full-term children several months after undergoing operation for ectopic pregnancy.

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## HABITUAL ABORTION

### A Pathologic Analysis of 100 Cases

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THE literature regarding habitual abortion is voluminous but comparatively few large series of cases have been reported. Moreover, most reports have dealt more with therapeutics than with pathogenesis. This study was undertaken, therefore, in the hope that a purely pathologic analysis of a comparatively large series of habitual abortions might afford valuable information for both the clinician and the pathologist. More particularly, it was desired to ascertain how often there was a common etiology in the successive abortions of a given patient.

#### Material

The material on which this study is based was collected from the pathologic records of the Boston Lying-in Hospital over a fifteen-year period (July, 1931, to July, 1946). The criteria used in selecting cases are as follows: Habitual abortion was considered to be a condition in which a woman has had two or more consecutive abortions before the twenty-eighth week of gestation. Each of these consecutive abortions must have been examined in the Boston Lying-in Pathology Laboratory, according to a standardized routine method of examination. Through the years, the method employed has been that first described by Mall and Meyer<sup>1</sup> with slight modifications, as discussed by Hertig and Edmonds.<sup>2</sup>

There was material from 123 patients which fulfilled these criteria. Further analysis revealed that, in twenty instances, either the history or the material submitted was inadequate for complete pathologic analysis. Three more cases were discarded because one of the two consecutive abortions in each case had been an ectopic pregnancy. There remain 100 patients with relatively complete clinical and pathologic records which form the basis of this study.

#### Results

The 100 patients selected according to the above criteria had a total of 220 abortions or 2.2 consecutive abortions per patient. There are 82 patients who have had two consecutive abortions, 16 who have had three, and 2 who have had four.

*Habitual Aborters Without Common Etiology.*—There are 42 patients in this group, representing 42 per cent of the series. Most of these patients had definite etiologies established for each of their abortions. There are, however, a small number of patients in whom a definite cause could not be ascribed for every abortion. In some of these abortions, the only pathology found was a grossly normal but macerated fetus. In others, a definite etiology could not be found because the material submitted from one abortion was insufficient for accurate diagnosis. The distribution of etiologies in this group was not statistically significant.

*Habitual Aborters With Common Etiology.*—There are 58 patients, or 58 per cent of the series, in this important group. The etiology for each specimen has been classified according to the method devised by Hertig and Livingstone<sup>3</sup> for their study of spontaneous abortions. Abortions with more than one possible etiologic factor have been classified according to the most significant pathology present. The distribution of repeated etiologies is shown in Table I.

TABLE I. NUMBER OF PATIENTS WITH HABITUAL ABORTIONS REPEATING THE SAME ETIOLOGY

	TWO SPECIMENS	THREE SPECIMENS	FOUR SPECIMENS	TOTAL PER CENT
<b>A. Ovular Factors</b> (43 cases)				
1. Pathologic ova	33	3	0	36
2. Fetal anomalies	1	1	0	2
3. Placental anomalies	4	0	1	5
<b>B. Maternal Factors</b> (15 cases)				
1. Uterine abnormalities	7	1	0	8
2. Inflammatory conditions	2	1	0	3
3. Miscellaneous	2	2	0	4

#### *Group A. Ovular Factors.*—

1. *Pathologic ova:* The only departure in this group from the classical types of Mall and Meyer<sup>4</sup> is the exclusion of grossly normal macerated features without evident etiology for the abortion. The pathologic or "blighted" ovum constitutes by far the largest group with common etiology. Thirty-six patients, representing 36 per cent of the total series or 62 per cent of the habitual abortions with common etiology, had pathologic ova. Twenty-seven of these had various types, nine having the same type of pathologic ovum in each abortion.

*Example (S-36-1187):* Past obstetric history revealed one normal full-term delivery. Her second and third pregnancies each terminated in the abortion of a Group III hydatid mole (Hertig classification).<sup>4</sup> This patient not only repeated a hydatidiform mole (a pathologic ovum in the strictest sense of the word) in both abortions but also presented the same type histologically in both cases.\*

2. *Fetal Anomalies.*—Two of our 100 cases, or 3.45 per cent of the 58 patients repeating the same etiology, were apparently due to fetal anomalies.

*Example (S-39-338):* The first examined abortion of this 34-year-old para 0, gravida I revealed an anencephalic monster of twenty-six weeks' gestational age. Nineteen months later she aborted a second anencephalic monster of the same gestational age. Her third pregnancy nine months after this resulted in another anencephalic monster aborted at 9 weeks' gestational age.

3. *Placental Anomalies.*—This group involved 5 of our 100 cases, or 8.62 per cent of the 58 repeating the same etiology. Table II lists the types of placental anomaly found in the twelve abortions of these five patients.

It will be seen that premature separation is the most common type among these patients. The only patient repeating the same type of placental pathology in two consecutively examined abortions had premature separation. The other four patients had combinations of different types of placental anomalies. One of these, having four consecutively examined specimens, serves as an excellent example of this group.

\*We also have the records from another hospital (not included in our series) of a patient who developed three moles consecutively.

TABLE II. TYPES OF PLACENTAL ANOMALY

Premature separation of the placenta	5
Placenta circumvallata	3
Hypoplasia of the placenta	2
Placenta membranacea	1
Breus' mole (subchorionic tuberous hematoma)	1

*Example (S-36-579):* Past obstetric history revealed a normal full-term delivery of her first pregnancy. A premature, seven months', otherwise uncomplicated delivery followed. Her next pregnancy resulted in the abortion of a normal fetus with a complete circumvallate placenta. Three succeeding pregnancies and abortions revealed in their respective order—a normal fetus accompanied by placenta circumvallata; a normal fetus with premature separation of the placenta and questionable low implantation; and lastly, a normal fetus in the presence of a complete circumvallate placenta.

#### Group B. Maternal Factors.—

1. *Uterine abnormalities:* This group constituted 8 per cent of the entire series and 13.8 per cent of the series repeating the same etiology. It is, therefore, second only to pathologic ova as a cause of habitual abortion among our patients. All of the fetuses and their placentas in this group were essentially normal. Furthermore, each of these patients repeated the same etiology in every abortion. These findings support the concept of uterine abnormality as a factor in habitual abortion.

The types of uterine abnormality found were retroversion, leiomyomas, low implantation of placenta including placenta previa, and abnormal fixation due to a previous Latzko section. This last abnormality was apparently responsible for three consecutive abortions of normal ova in one patient.

In analyzing the various types of uterine abnormalities, it might readily be said that each or all of the abortions due to these causes are theoretically salvageable and might have been saved, if each cause had been corrected. To prolong pregnancies involving low implantation until viability is reached might well be condemned. However, that prevention rather than treatment can be employed in some of these low implantations is well illustrated by one of the patients in our series. This particular patient had four abortions. The first two were recorded in her past obstetric history. The last two were consecutively examined, both revealing low implantation with premature separation. Following a uterine suspension for retroversion, she delivered a viable normal premature infant and a normal placenta. Whether this operative procedure prevented this particular pregnancy from aborting can only be surmised.

Low-implanted placentas are considered as a maternal or uterine factor rather than ovarian or placental because of the relatively high incidence of placenta previa in multiparas. This suggests that low implantations are due to some abnormality of the multiparous uterus rather than of the ovum per se. The two patients in our series who had low implantation, were both gravida III at the time of their first abortion.

The most common uterine abnormality was retroversion of the uterus, which was present in three of the eight patients.

*Example (S-44-938):* This 25-year-old, gravida I, had a spontaneous abortion the sixth week of her pregnancy. The fetus was normal. Nine months later she again aborted a normal fetus of twenty and one-half weeks' developmental age, according to its crown-rump length.<sup>5</sup> A third-degree incarcerated retroversion of the uterus was found.

2. *Inflammatory conditions:* This maternal factor accounts for three cases in our series, or 5.17 per cent of the 58 patients repeating similar etiology.

It is second only to the fetal anomaly group of two patients in being the least common factor in the series.

Two of these patients had two consecutively examined abortuses, the third having had three. Each of these patients had a combination of infections in each consecutive specimen rather than repeating the same type of inflammation.

Sterile decidual necrosis and marginal types of placentitis are not included in this series. The former is now recognized as one of a triad, along with thrombosis and hemorrhage of the decidua, found in most spontaneous abortions, while the latter is consistent with ruptured membranes of any appreciable length of time.

None of these inflammatory involvements were believed to have originated outside of the uterus, the infection being confined in each case either to the endometrium (decidua) or the placenta, with or without subsequent fetal infection. In view of this observation, one might well conceive the possibility of an induced abortion. However, this concept hardly seems feasible in this group of patients, since these abortuses were sent to the laboratory as a diagnostic problem in the therapy of habitual abortion.

*Example (S-35-1089):* The patient was a 34-year-old, gravida i, whose first pregnancy terminated in an abortion. The pathologic examination revealed an anatomically normal ovum of 9 and 5/7 weeks' developmental age, whose associated decidua showed acute bacterial inflammation due to gram-positive cocci. Sixteen months later, a normal ovum aborted completely at twelve weeks, apparently due to acute bacterial inflammation of the decidua and adjacent placental tissue. Streptococci were demonstrated by Gram stain in these tissues.

**3. Miscellaneous:** This group includes four patients in our series with three different common etiologies for their abortions. Two had endometriosis, one toxemia of pregnancy, and one hypothyroidism. Three of the four patients each representing a different type of etiology, are given below.

*Endometriosis (S-42-452):* This 28-year-old, gravida i, aborted a normal fetus of thirteen plus weeks' developmental age in April, 1942. In June, 1942, a laparotomy revealed extensive endometriosis as well as a pseudomucinous cyst of the ovary. The uterus was not removed because of the patient's desire for another pregnancy. In February, 1943, she again aborted a normal fetus of eighteen weeks' developmental age.

*Toxemia (S-44-407):* The past obstetric history revealed that the first pregnancy resulted in a normal living premature infant, the second in a seven months' stillborn infant, and the third in normal, full-term delivery. Two subsequent pregnancies terminated in abortions, both of which (examined in our laboratory) revealed a normal twenty-six week fetus with extensive placental infarction. The mother had a toxemia with all five pregnancies.

*Hypothyroidism (S-41-1172):* The past obstetrics history revealed that her first pregnancy, at 17 years of age, resulted in a normal, full-term living infant. Five abortions followed, all of which terminated at ten weeks' gestational age. Following the last of these abortions, she was seen as a sterility problem, at which time hypothyroidism was diagnosed and thyroid therapy instituted. In spite of this, three more abortions ensued, all at ten weeks, each of which was examined in our laboratory. The sixth abortion, the first examined specimen, revealed a pathologic ovum, group 3-A.<sup>1</sup> (While only a ruptured chorionic sac was found, a fetus presumably had originally been present.) The patient's seventh abortion was a slightly macerated, otherwise normal fetus of approximately eight weeks' developmental age. Her eighth abortion was an extensively macerated, but normally developed fetus of similar age. The accompanying products of conception of each abortus

revealed only immature placental tissue with decidual thrombosis, necrosis, and hemorrhage. Thus, in spite of known hypothyroidism with thyroid therapy for three years, three essentially normal pregnancies aborted, each at approximately ten weeks' gestational age. It is noteworthy that all abortions occurred at this stage of pregnancy.

### Discussion

Previously, 23 of the 123 patients in the initial series were excluded because of inadequate data. The omission of these 23 cases did not influence the statistical validity of this study. In the original series of 123 patients, 58.3 per cent of this number were found to repeat the same etiology. Following the exclusion of these patients, 58.0 per cent of the resultant 100 habitual aborters were found to repeat similar etiology, a variance of only 0.3 per cent.

Only 2 Rh-negative patients were present in the entire series and, in these 2 patients, other causative factors produced the repeated abortions. This finding is apparently in agreement with Hunt's<sup>6</sup> contention that the Rh factor plays little or no part as a cause of habitual abortion. However, many of our cases occurred before the discovery of the Rh factor and, hence, our data are not really significant with respect to this point.

The results of this study closely parallel those of 1,000 spontaneous abortions analyzed by the same technique,<sup>3</sup> thus affording an unusual opportunity for etiological and statistical comparison. Only those factors common to both series are included for comparison. The "miscellaneous" group is not a true comparison, because it includes different types of etiology in each study. It is included, however, merely for the sake of completeness. Table III presents a résumé of the etiology (repeated) in 100 habitual aborters versus the etiology (general) in 1,000 cases of spontaneous abortion.

Two interesting features are apparent from this comparison:

- (1) In both series, the percentages for any given factor are closely parallel.
- (2) In both series, all factors are in approximately the same proportion to one another.

The close relationship of these two series suggests that the etiological factor responsible for spontaneous abortion may also be responsible for habitual abortion.

If statistics are valid, and those involving this series have been found to be so,\* it becomes apparent that more than half of the 100 patients in our series, or 58 per cent, aborted repeatedly because of the same etiological factor.

TABLE III COMPARATIVE ETIOLOGY—HABITUAL VERSUS SPONTANEOUS ABORTIONS

	100 HABITUAL ABORTERS	PER CENT	1,000 SPONTANEOUS ABORTERS	PER CENT
<b>1. Ovular Factors:</b>				
a. Pathologic ova	36.		48.9	
b. Fetal anomalies	2.		3.2	
c. Placental anomalies	5.		9.6	
	—	43.	—	61.7
<b>2. Maternal Factors:</b>				
a. Uterine anomalies	8.		6.4	
b. Inflammatory conditions	3.		2.0	
c. Miscellaneous	4.		1.2	
	—	15.	—	9.6
	58		71.3	

\*The authors wish to express their appreciation to Miss Jane Worcester of the Harvard School of Public Health, Department of Biostatistics, for her review and analysis of all the material, including the statistics of this study. Her conclusion was that the statistical analysis of the material was significant and valid.

The significance of this finding becomes still more apparent if the statistics are more closely analyzed. A 58 per cent result in any series involving etiology would seem comparatively low compared to any other given series of cases. However, one should keep in mind that each of these 100 patients constitutes "a series within a series" in whom 2 or more abortions are involved and, when considered as such, the *collective* figure of 58 per cent repeating the same etiology is obviously quite significant. This figure might be still higher were it not for several patients in our series declared as not repeating similar causes simply because their abortuses could not be classified as to etiology.

In Table IV, the 58 patients repeating similar etiology are divided into three groups including those patients having two, three, and four consecutively examined specimens, respectively.

It is true that a division of our series into these three groups results in progressively smaller numbers for each, the statistical value in turn becoming only of relative importance. However, the definitely progressive rise in the incidence of repeated etiology in these three groups would seem to indicate that the more a patient aborts, the greater is her tendency to repeat the same etiology.

#### Summary and Conclusions

The etiology of all our large series of 100 habitual aborters varies both in extent and proportion, as does a series of 1,000 spontaneous abortions also studied in our laboratory. Individually, however, these habitual aborters repeated the same etiology in 58 per cent of the cases; 43 per cent being due to ovular factors and 15 per cent due to maternal factors. Pathologic ova were found to be the commonest etiology in habitual abortion, occurring in 62 per cent of the 58 cases. All other causes accounted for less than 10 per cent each of habitual abortions. Furthermore, the more often these patients aborted, the more often they repeated the same etiology.

TABLE IV. PROGRESSIVE INCREASE OF RECURRENT ABORTIONS AND THEIR REPEATED ETIOLOGY

1.	Number of patients with 2 consecutively examined abortuses	82.
	Repeating same etiology in both specimens	43.
	Percentage repeating same etiology	52.4
2.	Number of patients with 3 consecutively examined abortuses	16.
	Repeating same etiology in all 3 specimens	8.
	Repeating same etiology in 2 of 3 specimens	5.
	Total repeating same etiology	13.
	Percentage repeating same etiology	81.2
3.	Number of patients with 4 consecutively examined abortuses	2.
	Repeating same etiology in all 4 specimens	1.
	Repeating same etiology in 2 of 4 specimens	1.
	Total repeating same etiology	2.
	Percentage repeating same etiology	100.

The findings of our study would seem to warrant a revision of the approach to the clinical problems involved in habitual abortion. It should be evident that any woman who aborts is potentially an habitual aborter. Therefore, it is important that the very first abortus of any patient should be

thoroughly examined pathologically. This is apparently not often done, since many of the hundreds of records we have reviewed revealed previous abortions which had not been submitted for examination. The fact that, in our series, 99 per cent of habitual aborters returned repeatedly to the same clinic or physician demonstrates the feasibility of having all abortions examined pathologically as an aid to prognosis and therapy. By submitting all abortions to such examination, both the patient and her physician can become intelligently prepared for any subsequent abortions.

An increasing number of reports in the literature have appeared showing the satisfactory results from using specific therapy against certain factors causing recurrent abortions; for instance, the use of endocrinines in apparently forestalling the production of pathologic ova and vitamin E in preventing fetal anomalies. To give these treatments more rationale, the physician should know, whenever possible, whether the previous accidents of pregnancy were due to definite ovarian or maternal causes. An appeal for this approach, pointing out the means of obtaining it, is the essence of this study.

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221 LONGWOOD AVENUE.

## NECROPSY FINDINGS IN PATIENTS WITH CARCINOMA OF THE CERVIX

### Implications for Treatment

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IT IS generally inferred that fatality from carcinoma of the cervix is not the result of overwhelming dissemination of the disease, but rather to disturbances secondary to the presence of an advanced neoplasm in the pelvis, i.e., uremia from occlusion of the ureters, infection, or hemorrhage, or a combination of these factors. A perusal of the literature fails to reveal many reports with clear-cut data on this question.

In Pearson's<sup>1</sup> study of 57 autopsies of patients dying of carcinoma of the cervix, the most striking postmortem finding was stricture of the ureters, occurring in 75 per cent. Either pyonephrosis or pyelonephritis was present in 22 per cent. Uremic deaths occurred in 25 per cent. Peritonitis accounted for 19 per cent of the deaths. Distant metastases were present in only 25 per cent of the series.

DeAlvarez,<sup>2</sup> in summarizing the causes of death in 55 patients who died of carcinoma of the cervix, found the incidence to be ureteral obstruction in 40 per cent of the series; pulmonary causes in 31 per cent; and gastrointestinal causes in 13 per cent of the cases studied.

A review of the autopsy records in the Memorial Hospital from 1917 to the present, 1948, a period of thirty-one years, has shown protocols in 65 patients who died of cervical cancer. At first glance this would not appear to be a very large number, especially from a hospital devoted practically completely to neoplastic diseases. Furthermore, a low general autopsy incidence in the hospital would further contribute to the existence of such a small series. On the other hand, the inference is rather clear that cervical cancer is relatively slowly growing, and therefore an institution which could not serve as a center for terminal care would not be expected to have records in its autopsy files of patients whose final stages of disease were of relatively slow evolution—as seems to be the case in carcinoma of the cervix.

*Presence of disease beyond the pelvis at time of death:* Among the 65 necropsies, thirty-two presented macroscopic spread of disease beyond the pelvis. Of the latter, twenty-four had metastases to the periaortie nodes. In 9 per cent of these, the metastases appeared confined to these nodes, in the remainder there were also metastases elsewhere. The sites were: lungs and mediastinum, eleven; liver, six; cervical lymph nodes, three; miscellaneous foci including left adrenal gland, peritoneum, serosa of bowel, spleen, thoracic wall, peripancreatic nodes, subcutaneous tissue, and kidney. In six instances metastases were not described in the periaortie nodes.

The assigned causes of death were: uremia or pyonephritis, twelve cases; peritonitis, six; septicemia, four; tuberculous bronchopneumonia, one; empyema, one; intestinal obstruction, two; cause not stated, six.

*Death without metastases beyond the pelvis:* In the thirty-three subjects where macroscopically there were no metastases beyond the pelvis, death was ascribed to the following causes: peritonitis, ten; pelvic abscess, five; septicemia, two; pneumonia, two; septic pulmonary infarct, one; pulmonary embolus, one; pulmonary tuberculosis, one; pulmonary edema, one; uremia, six; hemorrhage into large bowel, one; pernicious anemia, one; cause not apparent, two.

*Disturbances of the urinary tract:* In forty-one of the sixty-five patients, irrespective of the presence of metastases beyond the pelvis, necropsy revealed some degree of ureteral obstruction with concomitant hydronephrosis. This would appear to be a part of the natural sequellae of uncontrolled cancer of the cervix, and as the latter continues to develop, the importance of the involvement of the ureters becomes progressively more significant, as regards the continued survival of the patient.

*Extent of cervical carcinoma at time of death:* Practically all of the patients in this series received irradiation therapy. Fifty-two presented residual or recurrent neoplasm in the cervix with or without pelvic or extrapelvic extension at the time of death. In six subjects there was no residual neoplasm in the cervix, but metastases beyond the pelvis were present. In five subjects there was no residual neoplasm in the cervix nor metastases macroscopically visible elsewhere. Death was due, among other things, to cirrhosis, one case, and extensive irradiation necrosis of pelvic tissues in five instances. No assignable cause for death was given in one case.

#### Discussion

The above data indicate that carcinoma of the cervix spreads beyond the pelvis primarily by lymphogenous metastases, the first extension being the periaortic lymph nodes. Following this a rather wide range of dissemination is manifested, as evidenced by the various localities of metastases, i.e., adrenals, spleen, liver, lungs, mediastinum, kidneys, etc.

As to treatment, the importance of some type of attack upon the lymphatic channels leading away from the cervix and out of the pelvis is strongly emphasized. The problem of purely local destruction of the primary growth is not much greater than the problem of blockage of the lymphatic pathways by which dissemination occurs. Irradiation therapy, it would appear, has limitations in this respect. Whether a systematic "en bloc" resection of the pelvic areolar tissue with lymph nodes and channels together with a pahysterection would yield improved results in the treatment of cervical cancer remains to be demonstrated, although theoretically, it is worthy of trial, inasmuch as a systematic surgical attack upon cervical cancer has not been carried out in recent years.

An important feature in the situation is the preservation of urinary tract function for as long as possible, since the data presented above, as well as in similar studies reported by others, reveals that a high incidence of immediate fatality is due to uremia caused by ureteral obstruction in the pelvis by the neoplasm. In the series reported above, 41 or 63% of the cases exhibited an appreciable degree of ureteral obstruction.

The factor of infection was an important one. General peritonitis, pelvic peritonitis, pelvic abscess and septicemia in varying degrees of combination were the immediate assignable causes of death in 24 patients, 38 per cent of the series. These were secondary to a recent operation, to a pelvic abscess complicating pelvic neoplasm, or secondary to necrosis of pelvic tissues from irradiation. The data are summarized in Table I.

TABLE I. SUMMARY OF DATA PRESENTED IN TEXT

Total number of necropsies, patients dying with primary diagnosis of carcinoma of the cervix	65 (100%)
Total number of patients presenting no gross evidence of spread beyond the pelvis at necropsy	33 (50% Plus)
Total number of patients presenting metastatic carcinoma beyond the pelvis at necropsy	32 (50% Minus)
Total number of patients with periaortic metastases as well as metastases elsewhere	24 (38.4%)
Total number of patients with periaortic metastases only	9 (13.8%)
Other sites of metastases:	
Lungs and/or mediastinal nodes	11 (18.4%)
Liver	6 (9.2%)
Cervical lymph nodes	3 (4.6%)
Extra-pelvic metastases in patients without periaortic nodes involved	6 (9.2%)
Number of patients found to have no residual neoplasm anywhere	5 (7.7%)
<i>Assigned causes of death</i>	
Cases without extrapelvic spread	
Peritonitis	10 (15.5%)
Pelvic abscess	5 (12.2%)
Septicemia	2 (3.1%)
Uremia	6 (9.3%)
Cases with extrapelvic spread	
Uremia or pyonephritis	12 (18.4%)
Peritonitis	6 (9.3%)
Septicemia	4 (6.2%)
Intestinal obstruction	2 (3.1%)
Uremia and/or pyonephritis—whole series	18 (27.7%)
Peritonitis and/or pelvic abscess—whole series	18 (27.7%)
Pelvic abscess and/or septicemia—whole series	6 (9.3%)
Cases with constriction of ureters (Those with and without fatal uremia)	41 (63%)

### Summary

In a review of 65 necropsies of patients who had carcinoma of the cervix, the following salient features appear deserving of emphasis:

1. Cancer of the cervix tends to spread primarily via the lymphatics, the periaortic nodes being first involved outside the pelvis in most instances.
2. Half of the patients died from various causes other than wide dissemination of the disease since necropsy revealed no gross evidence of neoplasm outside the pelvis in this group.
3. Uremia was the immediate cause of death in 27.7 per cent of the series, and ureteral obstruction of varying degrees was present in 63 per cent of the cases.

4. Infection, principally as peritonitis, pelvic abscess, and septicemia in varying combinations appeared to be the immediate cause of death in 38 per cent of the series. Thus uremia and infection together were the immediate causes of death in 66 per cent of the series, not widespread malignant disease.

5. Aside from eradication or restraint of the neoplasm, preservation of urinary tract function and avoidance of infection appear to be the principal problems to be dealt with for the prolongation of life in patients with cancer of the cervix.

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## **CYSTOSCOPY AND PYELOGRAPHY FOLLOWING PARAVESICAL EXTRAPERITONEAL CESAREAN SECTION**

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**T**HIS is a preliminary report of cystoscopic examination on a small number of cases (eighteen) following extraperitoneal section. The use of the extraperitoneal section has varied in its popularity, and for the most part over the years has been tried and then abandoned. Some surgeons have been expert in performing the operation, have no complaints to offer, and utilize the procedure frequently. Others have tried to perfect themselves in this technique, and, having encountered some difficulty, have become discouraged, and reverted to other means of delivery in the potentially infected or the frankly infected individual. Others have been deterred from attempting the operation because of objections raised against its use. A few of these objections are: (1) sharp dissection of the perivesical fascia lends to bladder and peritoneal perforation; (2) the bladder is markedly stripped of its fascia and nerve supply and that deformities and dysfunctions result therefrom; (3) there is too much handling of tissue and that the whole procedure is traumatic; (4) inability to be certain that the bladder has been removed from the lower uterine segment before incision of the uterus; (5) the removal of the bladder from the lower uterine segment so displaces the course of the ureters that ureteral injury may result by inadvertent incision of these structures; (6) the availability of sufficient room for the delivery of a large baby is markedly compromised; (7) the operation is too difficult and takes too long in the hands of the nonexpert. However, there are valid objections to the alternate choices used in the management of these cases.

Craniotomy is not without hazard, and bladder injuries with persistent fistulae may result, not to mention the serious damage to the soft parts when done by inexperienced hands. Porro section is a terrific price for the young primiparous individual to pay who wants a child. Many have claimed "excellent" results by doing a transperitoneal cesarean section and depending on all the sulfonamides and antibiotics available to stop or limit the spread of infection in the potentially or actually infected case. Such a series has not been reported, and it is our contention that if enough of cases are handled in this fashion there will be many that will not respond to the sulfonamides and antibiotics and that there will be an increase in the maternal morbidity and mortality.

We have at our command not a new type of extraperitoneal cesarean section, but a modification of the old Latzko type as described by Norton.<sup>1</sup>

His description has given us a better understanding of the pelvic fascia or areolar tissues, as some now prefer to call this tissue. In answer to the aforementioned objections he has done away with (1) sharp dissection of the perivesical fascia, instituting blunt finger dissection and minimizing bladder and peritoneal puncture. These accidents may still occur, but is the "hurried" and inexpertly "quick" hand that gets into trouble. The bladder (2) is not completely stripped of its fascia but it is freed especially at the upper left-hand corner and made mobile. Norton has suggested the term "chicken yellow fat" for the fat pad that is lateral to and common to all bladders, and he has pointed out that in this fatty area the perivesical fascia is weak and may be picked up with the fingers and bluntly stripped away from the anterior surface of the bladder. This fat has been mentioned by others, but it has never been stressed as a landmark for the initial step in the dissection of the bladder. The entire procedure of stripping the bladder anteriorly (3) requires but one and at most two manipulations. The next step requires the removal of the bladder from the lower uterine segment. This must be done with the bladder empty and a gauze pad protecting the bladder. This organ is pulled down to the symphysis and slightly to the right. The bladder with its base, which is still attached to the lower uterine segment, is again protected by a gauze pad held in place by a retractor before any incision in the uterus is made. (4) If there is any doubt at this point that the bladder is not completely removed from the lower uterine segment, then it is refilled with fluid and landmarks re-established. The posterior peritoneal fold must definitely be indentified and once it is, it is pulled up over the lower uterine segment using the periuterine fascia as a buffer. Norton advocates the use of a midline vertical uterine incision. If the incision is in the lateral portion of the lower uterine segment, the operator has not completely brought the bladder down and out of the way and the procedure is not being done correctly. (5) The uterine incision must be in the midline, thus it is not in proximity with either ureter, and the bladder base is amply protected with gauze pad and retractor. It is understood that the incision is made under direct vision and that blood and amniotic fluid must not obscure the operative field. (6) Sufficient room is obtained in the lower uterine segment by adequate elevation of the posterior peritoneal fold. (7) The average operating time for both attending and resident staff is forty minutes from skin to skin and ten minutes from skin incision to the delivery of the infant. The shortest elapsed time from skin incision to delivery of the infant in our hands has been just short of five minutes.

Since this operation is chiefly one of bladder dissection, it was thought necessary to test bladder function post partum. These patients were asked to return at about three months post partum for cystoscopic examination and for either intravenous or retrograde pyelography. The group consisted of fourteen private and 4 clinic patients, of which fourteen were primigravida and four were multigravida. The average length of labor was 33.4 hours and the average duration of ruptured membranes was 32.1 hours. Seven patients had

temperature elevations intra partum. A uterine culture was taken at operation in all cases and was positive for staphylococcus aureus, albus or streptococcus anhemolyticus in nine cases. There were seven cultures that showed no growth at the end of three days and two were not reported. The average baby weight was 3,200 grams. The one bladder puncture that we have had in the last 250 cases was seen in this group. This injury was done by one of the resident staff.

Each patient was questioned carefully on bladder symptoms:—frequency, urgency, incontinence with or without stress or strain. Two patients had frequency, one had urgency, one had incontinence with stress, and one had incontinence without stress (patient with the bladder injury). This patient with the bladder rupture will be discussed separately. On cystoscopic examination the bladder was filled with 300 c.c. of fluid to test its filling power. Each patient permitted that amount of bladder distention, but complained of fullness and urgency. Examination of the bladder wall showed a normal mucous membrane with no cystitis, the ureteral orifices were clearly visualized and each ureter was catheterized. The trigone in a few instances showed some hyperemia and various degrees of trigonitis. Cultures were taken from each kidney and all but two had sterile cultures. Each bladder seemed to have a normal contour on visualizing the interior. Intravenous or retrograde pyelography was carried out on each patient, and each has been reported as having a normal bladder shadow, normal ureters both in size and anatomic relationships, and normal kidney pelvis. The average time for dye excretion from each kidney was 3.3 minutes.

The patient with the bladder injury had been previously delivered vaginally after a prolonged labor of a living child, face presentation, weighing 3,200 grams. During this gestation she was admitted with a brow posterior, dipping into the pelvic inlet. At a sterile vaginal examination there was an attempted but unsuccessful conversion. The position now was an occiput transverse still in deflection attitude. After twenty-five hours of ruptured membranes and fifty-seven hours of desultory labor, the vertex was unengaged and the patient was morbid (temperature 102° F.). Under cyclopropane anesthesia, an extraperitoneal cesarean section was done. During the procedure the bladder was pierced by a finger, and this was due to the fact that the bladder was being removed from the lower uterine segment while it was still full. One must take time to empty the bladder if this accident is to be avoided. The bladder was repaired and postoperatively an indwelling catheter was left in place and continuous bladder drainage was maintained. The catheter was prematurely and mistakenly removed at the end of four days. On discharge from the hospital, it was noted that the patient had a vesicovaginal fistula. On her return three months later the fistula was still present. This could be seen on vaginal examination and was situated high on the anterior vaginal wall in the anterior fornix. Cystoscopic examination at this time showed a marked cystitis with a severe bullous edema of the mucosa. There was a hyperemia of the bladder interior especially in the region of the trigone. There was a traction diverticulum at the upper left-hand corner of the bladder at the site of the injury, and there was marked hypertrophy of the rugae. It was impossible to locate the ureteral orifices due to the edema present. At five months post partum the patient was again seen, and the fistula had completely healed spontaneously.

### Conclusions

1. The series is not of sufficient number to make too dogmatic statements, but it can be said that in the uncomplicated case where bladder injury does not occur, there is no impairment of bladder function, and no disturbance of bladder or ureteral anatomy.

2. With bladder injury, continuous drainage must be instituted and maintained until there is complete healing.
3. There have been no atonic bladders immediately postoperative or when seen at three months post partum.
4. Bladder manipulation is carried out on the empty bladder to avoid accidental puncture.
5. Uterine incision is in the midline and under direct vision so that even an anomalous or displaced ureter is not in the operative field.

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174 CLINTON AVENUE

## THE BACTERIOLOGY OF FALLOPIAN TUBES REMOVED AT OPERATION

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THIS investigation comprises a study of 72 patients from the wards and private service of the Women's Clinic of the Johns Hopkins Hospital. Seven patients had had a previous history of gonorrhreal infection, 40 had doubtful histories and 25 had negative histories.

In 1921 Curtis isolated the gonococcus from Fallopian tubes removed at operation in 38 of 192 cases, but gross and microscopically these tubes presented a picture of acute inflammation. Curtis also isolated *Escherichia coli*, streptococci, and anaerobic streptococci from cases of salpingitis and perisalpingitis. Cordua and Keek in 1926, reported isolating paratyphoid B bacillus from an ovarian abscess. In 1931 Worral reported having isolated Staphylococci from infected Fallopian tubes. Caussade and Giullemain, 1934, isolated the colon bacillus from the tubes of a 12-year-old girl. Brown, 1935, isolated *Salmonella newport* from a case of bilateral pyosalpinx. Studdiford, Casper, and Seadron, in 1938, reported isolating gonococci from the tubes of 16 of 24 cases studied. The organisms were isolated by culturing pieces of tissue and exudate, never from pus, and occasionally were degenerate in form but rapidly assumed the usual characteristics upon subculture. Thirteen of the specimens yielding gonococci showed pathologic evidence of subacute inflammation, two were acute exacerbations of chronic salpingitis, and one showed evidence of chronic or healed salpingitis with marked structural changes in the walls of the tube. According to Cornell, until 1934 there were 71 published cases of actinomycosis of the internal female genitals. American literature reported seven cases, English literature six, and the remainder were in other languages. Since then cases have been reported by Gardiner and Welsh, 1935; Côte and Tudhope, 1936; De Faria and Fiabio, 1937; Auster, 1940; and Ahumada and Chevalier, 1943.

### Technique

Immediately upon removal at operation the tubes were placed in sterile Petri dishes and brought to the laboratory. If pus or fluid was present in the tubes or abscesses a small area was seared with a searing iron, a sterile glass capillary pipette inserted, and the material aspirated for cultural study. Pieces of tissue were thoroughly ground in sterile sand and 3.0 c.c. of pancreatic digest broth, pH 7.2, for buried foci of infection. All specimens were cultured in the following manner: A tube of Brewer's sodium thioglycollate medium was inoculated and incubated at 37° C. for seventy-two hours. Smears were made every twenty-four hours and examined microscopically. Aerobic and anaerobic streak plates were made on pancreatic digest blood (rabbit) agar, the former incubated for seventy-two hours and examined every twenty-four hours and the latter incubated for forty-eight hours and then examined. For isolation of the gonococcus streak plates were made upon pancreatic digest chocolate blood (human) agar and incubated in an atmosphere of approximately 10 per cent carbon dioxide for forty-eight hours. This medium was used because it had been previously shown to be most satisfactory for the isolation of the gonococcus from cervical cultures, Koch, 1946. Direct

smears were made of all pus, exudate, and ground tissues, stained by Burke's modification of the Gram stain and examined microscopically. For final identification all organisms were thoroughly studied according to their biochemical reactions. A gonococcus complement fixation test was made upon each patient.

### Results

For convenience the patients in this study were grouped first according to the gross pathology of the Fallopian tubes (Table I) and second according to the histologic evidence of inflammation (Table II).

TABLE I. ORGANISMS ISOLATED FROM FALLOPIAN TUBES. ANALYSIS BASED UPON GROSS PATHOLOGY OF THE TUBES

TYPES OF CASES	TOTAL NO.	CUL-TURE STER-ILE	GROWTH						
			ALPHA STREPTOCOCCI	ANAEROBIC STREPTOCOCCI	HEMOLY. STAPH. AUREUS	STAPH. ALBUS	ESCH. COLI	ACTINOMYCES MURIS	MIXED CULTURES
Tubes enlarged, fimbria occluded	24	24	0	0	0	0	0	0	0
Tubes atrophic, fimbria occluded	1	1	0	0	0	0	0	0	0
Ovarian involvement, tubes occluded	18	14	0	1	1	0	0	1	1
Ovarian involvement, tubes patent	7	4	0	0	1	0	1	0	0
Lumen and fimbria patent	22	19	1	0	1	1	0	0	0
Totals	72	62	1	1	3	1	1	1	1

1. Twenty-four showed enlargement of the tubes with fimbria occluded. All cultures were sterile.
2. One showed atrophy of the tubes with fimbria occluded. Cultures were sterile.
3. Eighteen showed ovarian involvement with tubes occluded. Fourteen of these had sterile cultures, four yielded growth, one an anaerobic streptococcus, one hemolytic *Staphylococcus aureus*, one *Actinomyces muris* and the other a mixed multure of *Clostridium perfringens* and diphtheroids.
4. Seven showed ovarian involvement with tubes patent. Four yielded sterile cultures and three yielded growth, one hemolytic *Staphylococcus aureus*, one *Escherichia coli*, and one an unidentified very small Gram negative rod growing only in the presence of blood.
5. Twenty-two showed the lumen and fimbria to be patent. Nineteen had sterile cultures and three yielded growth, one *Streptococcus salivarius*, one hemolytic *Staphylococcus aureus*, and one *Staphylococcus albus*.

TABLE II. ORGANISMS ISOLATED FROM FALLOPIAN TUBES. ANALYSIS BASED UPON HISTOLOGIC EVIDENCE OF INFLAMMATION

TYPES OF CASES	TOTAL NO.	CULTURES STERILE	GROWTHII						
			ALPHA STREPTOCOCCI	ANAEROBIC STREPTOCOCCI	HEMOLY. STAPH. AUREUS	STAPH. ALBUS	ESCH. COLI	ACTINOMYCES MURIS	MIXED CULTURES
No evidence of inflammation	20	19	0	0	0	1	0	0	0
Subacute inflammation	31	26	1	0	1	0	1	0	1
Chronic inflammation	21	17	0	1	2	0	0	1	0
Totals	72	62	1	1	3	1	1	1	1

1. Twenty showed no evidence of an inflammatory process. Nineteen cultures were sterile and one yielded a growth of *Staphylococcus albus*.

2. Thirty-one showed evidence of subacute inflammation. Twenty-six yielded sterile cultures and five showed growth; one *Streptococcus salivarius*, one hemolytic *Staphylococcus aureus*, one *Escherichia coli*, one a mixed culture of *Clostridium perfringens* and diphtheroids and one an unidentified very small Gram negative rod growing only in the presence of blood.

3. Twenty-one showed evidence of chronic inflammation. Seventeen yielded sterile cultures and four showed growth: one an anaerobic streptococcus, two hemolytic *Staphylococcus aureus*, and one *Actinomyces muris*.

### Discussion

Pus producing organisms other than the gonococcus were isolated in 13.8 per cent or ten cases of the 72 patients studied; from 16.1 per cent of the tubes showing histologic evidence of subacute inflammation, and from 19.0 per cent of the tubes showing histologic evidence of chronic inflammation. That the gonococcus was not isolated was not surprising, since it is a known fact that the organism soon disappears from the tubal mucosa, and the Fallopian tubes studied in this survey showed no evidence of acute inflammation.

The four strains of hemolytic *Staphylococcus aureus* isolated, three from tubes and one from the pus aspirated from bilateral ovarian abscesses, were probably toxin producing strains, since all produced beta hemolysis on blood agar plates, fermented mannitol, liquefied gelatin, and were coagulase positive.

The patient yielding the Gram-negative unidentified rod from tubal cultures yielded *Hemophilus influenzae* from cultures of the pus from bilateral ovarian abscesses. Brucella agglutination tests were negative.

Two patients had positive gonococcus complement fixation tests. One patient had a recent history of gonorrhea; the other denied ever having been infected.

### Conclusions

1. In this study it was not possible to isolate the gonococcus from Fallopian tubes showing histologic evidence of subacute and chronic inflammation.

2. The Fallopian tube is not the focus of chronic gonorrhreal infection.

3. The gonococcus is short lived in the tubal mucosa and apparently produces a low level of demonstrable antibodies, since only one patient in the series of seven having histories of a previous gonorrhreal infection, and one patient in the 40 having doubtful histories had positive gonococcus complement fixation tests.

4. To my knowledge no other case has been reported in the literature of the isolation of *Actinomyces muris* (sometimes called *Streptobacillus moniliformis* and *Haverhillia multiformis*) from bilateral tubo-ovarian abscesses or of the isolation of *Hemophilus influenzae* from bilateral ovarian abscesses. If such cases have been reported, I have not been able to find them.

The author wishes to acknowledge the valuable assistance of Dr. J. Howard Brown and Dr. Richard W. Te Linde during this course of investigation.

Reports on the gross and histologic pathology of the specimens studied were obtained from the Pathology Laboratory of the Department of Gynecology.

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## PYELOURETERAL DILATATION OF PREGNANCY AFTER DEATH OF THE FETUS

### An Experimental Study

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**E**XPERIMENTALLY it has been shown that the fetus can be absent for months, or even the greater half of the normal length of gestation, without interrupting the physiologic state of pregnancy.<sup>1</sup> The fetus alone was removed, while the placenta was allowed to remain functional in the uterus, and when this was done in the latter half of pregnancy after the "hydroureter of pregnancy" had been established, the dilatation was seen to persist and even to progress, although the weight of the uterine contents had been diminished far below that which was attained before ureteral dilatation appeared.<sup>2, 3</sup> Weight of the uterus with its contents was even further disqualified as the primary cause of ureteral changes in pregnancy; for, when the fetus was removed at an earlier stage before obvious distention of the ureter had occurred, it was found that the hydroureter could arise and be maintained. The placenta under these experimental conditions was spontaneously expelled at a time compatible with the birth of a viable infant. Therefore, it appears that the normal duration of pregnancy as well as its characteristic hormonal levels<sup>4</sup> and the onset of contractions associated with the expulsion of uterine contents at term, are independent of the presence of the fetus. This experimental work was carried out in the rhesus monkey (*Macaca mulatta*), a primate with a twenty-eight day menstrual cycle and whose genital tract and reproductive physiology are strikingly like that of man.

After the study of several hundred pregnancies in the monkey, we now have three instances in which there was spontaneous death of the fetus from some inherent cause while the placenta remained hormonally active in relation to the mother organism. Thus, the essential factors of the earlier experimental work were duplicated. Pregnancy in the rhesus monkey lasts about six months, and the first evidence of a fetal skeleton is seen around seventy days. It is routine to make x-ray films of all pregnant animals at this time with added films before or later, according to the problem under consideration. The progress of pregnancy before the appearance of the fetal skeleton is followed by rectal palpation of the enlarging uterus and by x-ray films after intravenous injection of an opaque medium\* which, when excreted by the pregnant animal, gives good visualization of the hilus and full length of the ureter in most cases. In the nonpregnant animal the contrasting medium passes through

\*Diodrast was generously supplied by the Winthrop Chemical Company, Inc.

to the bladder so quickly that traces alone can be seen in the ureters. Only after the establishment of the definitive placenta about the thirty-fifth day,<sup>5</sup> do the ureters fall under the hormonal influence exercised by that organ upon all smooth muscle. A slowing up of the urinary flow is a sign of pregnancy.

*Monkey A.*—Jan. 18, 1940, was the conception date initiating this pregnancy, first recognized on rectal palpation February 17. This was the second gestation for the animal born in the laboratory in 1935. The routine urogram on the seventy-sixth day of pregnancy showed an enlarging uterus but no skeleton. There was a definite distention of the right ureter and suggestive changes in the left. Both ureters were well visualized, indicating a moderate stasis. A second x-ray (Fig. 1) was taken on the ninety-fourth day of pregnancy.



Fig. 1.—X-ray photograph showing distended ureter in a monkey on the ninety-fourth day of pregnancy. Interrupted line marks extent of uterus.

The distended right ureter was seen, but the uterine shadow was not large enough to be compatible with a normal gestation of this length and no fetal skeleton was evident. A hysterotomy was performed on the one hundredth day and the uterine contents removed as a whole. The placental size was comparable to that of a sixty-day pregnancy, but when the membranes were opened no fetus was found, although the point of attachment of the cord was easily recognized. The amniotic fluid contained some debris. In this instance, even after spontaneous absorption of the fetus, the hydroureter persisted because of the presence of a functioning placenta. At eleven days post partum, the ureters were normal in size.

*Monkey B.*—This animal matured in the colony, menarche on Sept. 30, 1938. The first ovulation was recorded as having taken place a few days before a laparotomy performed six months later on March 14, 1939. The first pregnancy began November 8 and is the one of

interest here. The animal was in a group being studied for the character of ureteral response in known first pregnancies. An x-ray film on the thirty-sixth day visualized the ureters, which were normal in caliber for the nonpregnant animal, but the unbroken columns of fluid indicated placental activity. Three weeks later, on day fifty-nine, these columns were seen to have doubled their width, indicating a beginning of dilatation. The fundus of the uterus reached the lower border of the seventh vertebra and the pregnancy, as disclosed in these two x-ray pictures, appeared to be progressing normally. However, on the eighty-eighth day the uterine shadow, which then extended to the upper border of the seventh vertebra, did not contain any evidence of a fetal skeleton. An x-ray picture taken of this animal on the eightieth day of a normal pregnancy during the following year was used for comparison and in the normal picture the uterus was larger reaching the central zone of the fifth vertebra. In the normal pregnancy the outlines of the skull and facial bones lay to the right of the sixth lumbar vertebra with the axial skeleton of the fetus distinguishable between the seventh vertebra and the crest of the ilium. Ureteral distention was definitely less than in the pathologic pregnancy under examination here in which there was a much smaller uterus. A hysterotomy was performed upon the one hundred twenty-seventh day in order to recover and examine the uterine contents. Without opening up the amniotic cavity, the placenta with its membranes was dissected from the uterine wall and placed in formalin to harden before opening. The embryo measured 25 mm. When the length of the embryo was taken with its physical appearance and reference made to Heuser and Streeter's<sup>6</sup> work (1941), it was indicated that the stage of development reached was about the forty-sixth day. This agrees with data from our own series of fetuses. The placenta weighed 47 grams, a weight which is normally associated with a pregnancy of seventy-five days' duration. A fetus compatible with a seventy-five day pregnancy should measure about 90 mm. (Schultz<sup>7</sup>) in length instead of the aforesaid 25 mm. and so it appears that the failure began in the embryo while the placenta continued to function, in part. To summarize, in this animal there was an established ureteral dilatation on the fifty-ninth day, two weeks after the death of the fetus, and the dilatation persisted through the eighty-eighth day, or seven weeks after the fetal death, and up to eleven weeks later to the time of the hysterotomy on the one hundred twenty-seventh day. Thus, the living, functioning placenta sustained the physiological state of pregnancy with its accompanying hydroureter for 81 days after the death of the embryo.

*Monkey C.*—Born in the laboratory May 21, 1937, the first pregnancy of this animal began Feb. 4, 1940. On the ninety-fourth day the urogram showed columns of fluid with some distention of the ureter. There was no fetal skeleton and the uterine fundus reached only to the upper part of the body of the sixth vertebra. The diagnosis of fetal death before the seventieth day was made. The animal was kept under close observation, especially when vaginal bleeding began on the one hundred twenty-first day. Twenty-four hours later it was possible to recover the products of the spontaneous, complete abortion. On examination it was found that the primary and secondary lobes of the placenta were well defined, but the ovum was represented by a pear-shaped solid mass 1.5 cm. in diameter within a collapsed amniotic sac. The size of the placenta indicated comparatively normal growth to about the sixtieth day. The embryo gave no clue to the stage reached before degeneration, but the well-defined placenta indicates embryonic normality for fifty days or more. It is of interest to compare the ureteral dilatation of this pregnancy with that of the succeeding one. Comparison was made with a urogram of the one hundred forty-eighth day from the second pregnancy. At this time the height of ureteral distention for the pregnancy should be reached and it was interesting to find that, even in the presence of a comparatively large fetus, the dilatation was less in degree than in the first pregnancy at ninety-four days with a degenerated fetus.

### Discussion

When hormone assay methods were first available, Frank,<sup>8</sup> 1929, studied a case in which the placenta had remained in the uterus for eighteen days following an otherwise normal delivery. Before manual removal of the placenta the

estrogen level of the blood was found to be characteristic of pregnancy. In a study of an abdominal pregnancy after a term fetus had been removed and while of necessity the placenta had been left attached to the viscera, Ware and Main,<sup>9</sup> 1934, showed that the patient remained physiologically pregnant for over a month following removal of the infant. At the end of that time the urine assays for prolan became negative and it was assumed that the placenta had been absorbed.

Zondek<sup>10</sup> has recently described a human case in the eighth month of pregnancy in which fetal movements had ceased—no fetal heart sounds were heard and death of the fetus was diagnosed. Hormonal tests, however, showed that the level of estrogenic hormone in the serum corresponded to that of normal pregnancy, and the gonadotropin level of the urine was also high. These values fell only after operative removal of a dead fetus with a placenta normal in appearance. The work<sup>4</sup> from our laboratory has shown that after operative removal of the fetus the estrogenic levels were maintained until spontaneous expulsion of the placenta, after which the estrogens fell abruptly but the androgens, coming in greater part presumably from the adrenals, returned more slowly to the nonpregnant levels. Zondek says, in remarking on the fact that the placenta can sometimes remain functional in spite of death of the fetus, "In such cases the hormone levels in blood and urine can be higher than in normal pregnancy because the entire output of placental hormones is taken up by the maternal circulation, none going to the fetus." In this connection it is interesting to note the early appearance of dilatation present on the fifty-ninth day in Monkey B.

Within the last year Hirsch<sup>11</sup> has described a case of convulsive eclampsia in which all signs and symptoms developed after death of the fetus. He warned against complacency, even though the fetus was known to be dead because the placenta might still be active.

Evidence for the functional independence of the placenta, once pregnancy is well started, is imposing. It has long been known that ovaries are not necessary for the completion of pregnancy in the human being and Hartman and Corner<sup>12</sup> have recently, in the monkey, pushed back the crucial time for removal of the ovaries (corpus luteum) to the first month of the six-month gestation. In the same animal it has been shown<sup>1</sup> that the operative removal of the fetus or the fetus with one or both ovaries does not interrupt pregnancy; thyroidectomy is compatible with the continuance of gestation and, in some animals finally, P. E. Smith<sup>13</sup> has shown that the hypophysis is not necessary for the continuation of pregnancy. A comprehension of the autonomy of the placenta has developed with the accumulation of data from the field of endocrinology.

### Summary

Upper urinary tract dilatation has been demonstrated in the monkey after death of the fetus, but while the placenta remained functional toward the maternal organism. The unruptured uterine contents were secured at hysterotomy in two instances and recovered at the time of a spontaneous abortion in the third.

These three histories of primary death of the fetus parallel earlier experiments in which the fetus alone was surgically removed. Thus, pyeloureteral dilatation in pregnancy is associated with the functioning of the maternal surface of the placenta during the physiological state of pregnancy without dependence on the continued presence or life of the fetus.

Grateful acknowledgment is made to Mr. Joseph Negri for management of the monkey colony, and to Miss Janet Buchanan and Miss Helen Carlson for the excellent urographs.

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## A STATISTICAL REPORT OF 1,771 CASES OF HYSTERECTOMY

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ON THREE previous occasions, statistics on hysterectomy have been presented from this department.<sup>1-3</sup> This fourth report comprises 1,771 consecutive cases covering the five-year period ending Jan. 1, 1945. The pan- or total hysterectomy as described by W. H. Weir<sup>4</sup> has been the procedure of choice.

As seen in Table I, panhysterectomy was done in 71 per cent of the cases. This is slightly lower than in our previous series, due to the recent popularity of the vaginal hysterectomy, which shows a proportional increase. The supravaginal hysterectomy was done on only the most complicated cases by the resident staff, but continues to be a routine procedure by a few of the visiting staff, which accounts for the relatively high number in the latter group. Although the proportion of white to Negro in the community as a whole is ten to one, 30 per cent were Negro patients. This is due to the

TABLE I. DISTRIBUTION OF CASES

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
<i>Distribution.—</i>								
Resident staff	82	4.63	59	3.33	580	32.7	721	40.7
Visiting staff	97	5.48	260	14.7	693	39.2	1,050	59.3
Combined staffs	179	11.1	319	18.0	1,273	71.0	1,771	100.0
<i>Color distribution.—</i>								
White	159	88.8	258	80.9	822	64.5	1,239	69.9
Negro	20	12.2	61	19.1	451	35.5	532	30.1
<i>Parity.—</i>								
Para 0	6	3.4	138	43.4	413	32.4	557	31.4
Para 1 plus	173	96.6	181	56.6	860	67.6	1,214	68.6

greater incidence of myoma and pelvic inflammation in this group and to the particular district from which the out-patient clinic draws the majority of its cases. The greater proportion of parous patients is again found in the vaginal hysterectomy group where prolopse resulting from childbirth is the most frequent indication for this procedure. As a supravaginal hysterectomy is usually done only in the presence of a normal-appearing cervix, a comparatively larger number of nonparous women are found in this group.

The age distribution is given in Table II. The largest proportion of the pan- and supravaginal hysterectomies occurs in women nearing or at the menopause, namely, in the fourth and fifth decades of life. This is due to many factors including the increase in symptoms from pathologic lesions of

the pelvic organs at this age, the often elective nature of this operation, and the desire to preserve the reproductive function by most women as long as possible. As prolapse is usually a late complication of childbirth, vaginal hysterectomy is done more often in the later decades.

TABLE II. AGE DECADE DISTRIBUTION

YEARS	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	CENT PER	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Second decade, 10 to 19	0	0	1	.31	5	.39	6	.28
Third decade, 20 to 29	2	1.1	18	5.6	73	5.7	93	5.2
Fourth decade, 30 to 39	27	15.1	131	41.0	540	42.4	698	39.4
Fifth decade, 40 to 49	48	26.8	136	42.6	542	42.6	726	41.0
Sixth decade, 50 to 59	57	31.8	27	8.5	90	7.1	174	9.8
Seventh decade, 60 to 69	39	21.8	6	1.9	22	1.7	67	3.8
Eighth decade, 70 plus	6	3.4	0	0	1	.08	7	.4

Chronic cervicitis has been excluded from the list of diagnoses given in Table III because its presence was reported by the pathologist in almost every case in which the cervix was examined. Myoma and relaxation of the vaginal outlet again are the most common indications for hysterectomy. The incidence of salpingitis has not appreciably decreased as yet as a result of penicillin and the sulfonamides, because old, chronic cases originating before the advent of these drugs were most often encountered. The diagnosis of endometriosis was not confirmed by the pathologist in many cases but was made clinically at the time of operation, on finding extensive and characteristic scar tissue from which the islands of endometrial-like glands had long since disappeared. The four instances of carcinoma of the cervix were diagnosed postoperatively.

TABLE III. INCIDENCE OF DIAGNOSIS

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Relaxed vaginal outlet	172	96.0	95	29.8	635	49.8	902	52.0
Myoma	61	34.0	258	89.3	897	70.5	1,216	68.5
Salpingitis	1	.56	93	29.2	375	34.0	469	26.5
Endometriosis	10	5.6	56	17.6	176	13.8	242	13.7
Ovarian tumors	1	.56	26	8.1	58	4.5	85	4.8
Carcinoma of fundus	2	1.1	7	2.2	24	1.9	33	1.9
Carcinoma of cervix	0	0	1	.31	3	0.2	4	0.2
Prolapse	165	92.2	7	2.2	111	8.7	283	16.0

TABLE IV. DISTRIBUTION OF MOST COMMON SYMPTOMS

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Pain	123	68.7	229	71.8	872	68.5	1,224	69.1
Bleeding	33	18.4	142	44.5	580	45.5	775	42.6
Tumor	0	0	39	8.2	126	9.9	165	9.3
Prolapse	103	57.6	1	.31	23	1.8	127	7.2

It is difficult to evaluate the frequency of the symptoms, due to their variety and their subjective character. Those tabulated in Table IV are, at best, only an estimation. Urinary symptoms, although found very frequently and, in few cases, as the primary one, were excluded because they are most often secondary.

Additional operative procedures at the time of hysterectomy are not only frequently desirable but are often necessary. The incidence in this series is shown in Table V. To obtain the best clinical result by providing adequate pelvic support, the repair of the relaxed vaginal outlet is considered of primary importance in this clinic. The frequency of repair procedures approximates the incidence of relaxed vaginal outlets and approaches that of parous women. As active infection is rare in this type of pelvic surgery, appendectomy is not only desirable but can be easily done and frequently is.

TABLE V. ADDITIONAL OPERATIVE PROCEDURES

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Curettage	4	2.24	29	9.1	50	3.9	83	4.7
Perineorrhaphy	174	97.2	90	28.2	620	48.6	884	49.9
Anterior colporrhaphy	177	98.8	35	11.0	291	22.8	503	28.4
Partial removal of adnexa	4	2.24	128	40.1	414	32.4	546	30.8
Complete removal of adnexa	1	.56	46	14.4	260	20.4	307	17.3
Appendectomy (possible)	0	0	159	68.5	862	86.3	1,021	82.9
Hemorrhoidectomy	26	14.5	23	7.2	83	6.5	132	7.5
Cholecystectomy	0	0	0	0	1	.08	1	.06

Injury to the bowel or bladder at the time of operation, though infrequent, as seen in Table VI, is seldom serious. On the other hand, a cut or tied ureter is the most feared operative complication of hysterectomy. Consciousness of this danger has kept the incidence very low, although it is slightly higher here, when compared with our previous five-year period. Contrary to the popular belief of the general surgeon, its occurrence is no higher in the pan- or total hysterectomy than it is in the supravaginal.

TABLE VI. OPERATIVE COMPLICATIONS

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Injured ureter	1	.56	3	.93	7	.55	11	.62
Torn bladder	0	0	0	0	8	.63	8	.45
Torn bowel	2	1.1	2	.62	5	.39	9	.51

Various postoperative complications are enumerated in Table VII. They are all relatively infrequent. While the incidence of infected wounds and cystitis is lower, the others remain essentially the same as in the previous five-year period and are again approximately the same in the supravaginal and panhysterectomies. Paralytic ileus, which is now more easily recognized and treated, was a complication in 1.7 per cent of the cases.

TABLE VII. POSTOPERATIVE COMPLICATIONS

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Infected wound	1	.56	12	3.76	36	2.8	49	2.8
Peritonitis	3	1.7	2	.62	8	.63	13	.73
Phlebitis	1	.56	1	.31	12	.94	14	.79
Vesicovaginal fistula	0	0	0	0	2	.16	2	.11
Rectovaginal fistula	1	.56	0	0	2	.16	3	.17
Pulmonary embolus	3	1.7	2	.62	9	.71	14	.79
Cystitis	16	8.3	11	3.4	46	3.6	73	4.1
Pyelitis	1	.56	2	.62	3	.24	6	.34
Pneumonia	3	1.7	1	.31	14	1.1	18	1.0
Paralytic ileus	2	1.1	7	2.2	21	1.7	30	1.7
Hemorrhage	2	1.1	2	.62	12	.94	16	.9

TABLE VIII. MORBIDITY

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Temperature below 38.5° C.	74	41.4	170	53.3	763	59.9	1,007	56.8
Temperature above 38.5° C. for one day	39	21.7	82	25.7	257	20.2	378	21.3
Temperature above 38.5° C. for more than one day	66	36.9	67	21.0	253	19.9	386	21.8

The conventional method of reporting morbidity rates is used in Table VIII. It is not completely satisfactory because of the large number of cases which have a brief, twenty-four to forty-eight hour, but marked febrile reaction postoperatively, for which there is no adequate explanation. The morbidity in the vaginal hysterectomy group, because of the more advanced age of the patients, remains essentially the same as before and is higher than that found in the supravaginal and panhysterectomy groups. These are appreciably lower than those reported previously, due probably to the availability and more frequent use of the sulfonamides and penicillin.

TABLE IX. MORTALITY RATES

	179 VAGINAL HYSTERECTOMY		319 SUPRAVAGINAL HYSTERECTOMY		1,273 PAN- HYSTERECTOMY		1,771 TOTAL	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Resident staff	0	0	2	4.08	8	1.38	10	1.37
Visiting staff	3	3.2	1	.38	6	.87	10	.95
Combined staffs	3	1.68	3	.93	14	1.10	20	1.13

The mortality rates are shown in Table IX. These compare favorably with similar series of hysterectomies and our last one. The mortality rates for supravaginal and panhysterectomies are approximately the same and for the vaginal hysterectomies only slightly higher. A brief summary of the

primary cause of death is as follows: Of the fourteen deaths following pan-hysterectomy, one was due to pneumonia, four to pulmonary embolus, four to peritonitis, and five were due to cardiac failure. Of the three deaths following supravaginal hysterectomy, one was due to pulmonary embolus, one to cardiac failure, and one to cerebral hemorrhage. Finally, of the three deaths following vaginal hysterectomy, one was due to pulmonary embolus, one to cerebral accident, and one to peritonitis.

In conclusion, statistics have been presented on a large number of consecutive hysterectomies for another five-year period from this department. Although it is generally conceded that, in trained hands, pan- or total hysterectomy as against supravaginal hysterectomy is the procedure of choice when the uterus is to be removed, our statistics again bear this out.

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## THE RATE OF RENEWAL IN WOMAN OF THE WATER AND SODIUM OF THE AMNIOTIC FLUID AS DETERMINED BY TRACER TECHNIQUES

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ALTHOUGH the injection of dyes has demonstrated that exchange of an artificial constituent of the amniotic fluid may take place with the maternal plasma,<sup>1, 2</sup> it was impossible to obtain a reliable and precise picture of the dynamics of the naturally occurring constituents of the fluid until radioactive and stable isotopes became available for experimental purposes. Measurements made with the isotope technique in the guinea pig showed that the water of the fluid at all stages of gestation is completely replaced at the surprisingly rapid rate of about once an hour, whereas the rate of replacement of the sodium is about fifty times slower.<sup>3</sup> We have now measured water and sodium transfer to the human amniotic fluid using deuterium oxide (heavy water) and radioactive sodium ( $\text{Na}^{24}$ ) as the tracer substances. The observations with water were made on five women, and with sodium on twenty women, on whom hysterotomies were performed for the reasons given in Tables I and II.

### Methods

The cases in this series are the same as those used in measurement of placental transfer of water and sodium to the fetus; and details of the techniques employed can be found in the reports of those studies.<sup>4, 5</sup> The essential points are: (1) A sample of amniotic fluid was withdrawn through the wall of the intact uterus with needle and syringe approximately thirty minutes after intravenous injection of NaCl tagged with  $\text{Na}^{24}$ , and ten minutes after intravenous injection of deuterium oxide ( $\text{D}_2\text{O}$ ). (2) Care was taken to avoid contamination of the fluid with blood. (3) The rate of disappearance of the tracer substance from the maternal blood plasma was determined for the tagged sodium and  $\text{D}_2\text{O}$  in order to permit calculation of the average concentration of the tracer during the period of transfer to the amniotic fluid. The  $\text{D}_2\text{O}$  content of each sample of amniotic fluid was determined in duplicate; checks to within  $\pm 0.01$  per cent were obtained. Because of the low concentration of tagged sodium, radioactivities were measured on samples of 5 c.c. of amniotic fluid or, in some cases, on larger samples concentrated by evaporation; correction was made for absorption of radiation by the sample.<sup>6</sup>

The methods and rationale for calculating the rate of transfer of water and sodium to the fetus have been given.<sup>4, 5</sup> Similarly, the amount of water trans-

TABLE I. RATE OF TRANSFER OF WATER FROM MATERNAL CIRCULATION TO AMNIOTIC FLUID.  
 "DELIVERY TIME OF AMNIOTIC FLUID" REFERS TO MINUTES AFTER INJECTION  
 OF D<sub>2</sub>O INTO MOTHER

INDICATION FOR OPERATION	GESTATION AGE WEEKS	DELIVERY TIME OF AMNIOTIC FLUID MINUTES	AVERAGE CONCEN-	CONCEN-	H <sub>2</sub> O TRANS-	PER CENT OF H <sub>2</sub> O OF AMNIOTIC FLUID RENEWED
			TRATION OF D <sub>2</sub> O IN MATERNAL PLASMA PER CENT		FERRED PER C.C. OF AMNIOTIC FLUID PER HOUR	
Chorea	14	7.5	0.616	0.029	0.376	37.6
Psychiatric	16	9.5	0.448	0.019	0.269	26.9
Cardiac disease	18	11.0	0.447	0.011	0.134	13.4
Chronic pyelitis	30	5.2	0.485	0.031	0.740	74.0
Contracted pelvis	40	7.1	0.411	0.010	0.206	20.6
					Average	34.5

TABLE II. RATE OF TRANSFER OF SODIUM TO AMNIOTIC FLUID FROM MATERNAL CIRCULATION.  
 "DELIVERY TIME OF AMNIOTIC FLUID" REFERS TO MINUTES AFTER INJECTION OF Na\* INTO MOTHER. THE RADIO-ACTIVITIES WERE MEASURED IN SAMPLES LARGER THAN 1 C.C. BUT ARE PRESENTED IN THIS UNIT FOR CONVENIENCE. IN CALCULATING "PER CENT OF Na OF AMNIOTIC FLUID RENEWED PER HOUR," IT WAS ASSUMED THAT 1 C.C. OF AMNIOTIC FLUID CONTAINS 2.8 MG. Na (6)

INDICATION FOR OPERATION	GESTA-TION AGE WEEKS	DELIVERY TIME OF AMNIOTIC FLUID MINUTES	Na* PER C.C.	Na* PER C.C.	Na TRANS-	PER CENT OF Na OF AMNIOTIC FLUID RENEWED
			MATERNAL PLASMA (AVERAGE) MICROGRAMS		FERRED PER C.C. AMNIOTIC FLUID PER HOUR	
Previous section	38	30	1.94	0.056	0.189	6.8
Psychiatric	16	25	1.31	0.025	0.151	5.4
Psychiatric	10	29	1.74	0.029	0.112	4.0
Previous section	37	26	5.98	0.079	0.101	3.6
Previous section	40	42	3.60	0.340	0.440	15.0
Chorea	14	28	3.23	0.022	0.048	1.7
Contracted pelvis	36	27	2.59	0.041	0.116	4.1
Chronic pyelitis	31	40	3.80	0.280	0.370	14.0
Carcinoma, abdomen	17	28	3.86	0.086	0.157	5.4
Contracted pelvis	40	27	5.22	0.127	0.179	6.4
Epilepsy	12	28	4.65	0.186	0.282	10.0
Chronic nephritis	12	30	5.84	0.030	0.034	1.2
Hypertension	16	28	4.00	0.044	0.078	2.7
Hypertension	24	26	0.61	0.013	0.164	5.8
Hypertension	20	26	4.00	0.130	0.240	8.6
Hypertension	38	28	3.02	0.170	0.398	15.0
Pre-eclampsia	18	27	0.30	0.007	0.171	6.1
Pre-eclampsia	31	29	6.10	0.380	0.420	15.0
Cardiac disease	19	27	5.20	0.084	0.119	4.3
Cardiac disease	18	33	2.25	0.034	0.091	3.3
					Average	6.9

ferred to 1 c.c. of amniotic fluid in a known interval of time can be calculated from the equation:

$$H_2O_{amf} = D_2O_{amf} \div D_2O_{mb}$$

where H<sub>2</sub>O<sub>amf</sub> represents the water transferred to 1 c.c. of amniotic fluid; D<sub>2</sub>O<sub>amf</sub>, the observed concentration of heavy water in the water of the amniotic fluid; D<sub>2</sub>O<sub>mb</sub>, the average concentration, during the period of the experiment, of heavy water in the water of the maternal blood. The average concentration of heavy water in the water of the maternal blood is used in the calculations because of

the rapidly diminishing concentration of  $D_2O$  in the blood during the early part of the experiment. The method for obtaining this value has been reported.<sup>4, 5</sup> In like manner the amount of sodium transferred to the amniotic fluid for the period of the experiment can be calculated from the equation:

$$Na_{amf}^* = Na_{amf}^* \times Na_{mp} \div Na_{mp}^*$$

where  $Na_{amf}^*$  refers to the sodium, tagged with the radioactive isotope, which is present in 1 c.c. of the amniotic fluid;  $Na_{mp}^*$  to the average concentration of tagged sodium in the maternal plasma and  $Na_{mp}$  to the concentration of normally occurring sodium in the maternal plasma. We have assumed the concentration of sodium in maternal plasma to be 3.3 mg. per cubic centimeter.<sup>7</sup> The calculation of the rate at which the sodium of the amniotic fluid is replaced by sodium of the maternal plasma has been made on the assumption that there are 2.8 mg. sodium per c.c. amniotic fluid.<sup>8</sup>

### Results

The results are presented in Tables I and II and call for little comment. On the average, 34.5 per cent of the water of amniotic fluid is replaced per hour by water from the maternal plasma. This means that the average rate of renewal of the water of the amniotic fluid is once every 2.9 hours. The sodium of the fluid is renewed at the average rate of 6.9 per cent of that present per hour; i.e., the sodium of the fluid is turned over once every 14.5 hours. There is considerable variation, apparently unrelated to gestational age, among the observed rates both for water and sodium.

### Discussion

The rate at which water is transferred to the amniotic fluid is considerably greater than that for sodium. Whereas the amount of water which flows into and out of the amniotic sac in three hours is approximately equal to the volume of the amniotic fluid, only about one-fifth of the total sodium is replaced in the same interval. This means that water is renewed about five times as rapidly as sodium. When a comparison of the rates of transfer of water and sodium across the placenta in the guinea pig was made, a similar difference was noted.<sup>9</sup> Evidence was given which could explain the observations completely on the basis of greater permeability of the placental membrane to water than to sodium. The same explanation, applied to whatever membranes are involved, may hold for the difference in transfer rates of water and sodium from the maternal circulation to the amniotic fluid.

It will be apparent from the large difference in rate of transfer of water and sodium to the amniotic fluid that it is impossible to make reliable deductions about the rate of exchange of the normal constituents of the fluid from observations on foreign substances like dyes.

The main source of the amniotic fluid has been thought by some investigators to be fetal urine. The present experiments shed no light as to the principal site at which the exchange of water and sodium between the maternal blood and amniotic fluid takes place. It was pointed out in studies on the guinea pig<sup>8</sup> that in the earlier stages of pregnancy a volume of water equal to that of the fetus flows in and out of the amniotic sac in an hour, and that it would seem questionable that the fetal urine could alone account for this relatively large volume of fluid. The results in women substantiate this view. At the tenth week of gestation, for example, 40 c.c. of amniotic fluid may be associated with

a fetus weighing less than 20 Gm.<sup>8</sup> and the water of this fluid will be completely replaced in about three hours. At term a fetus weighing 3.4 kg. is surrounded by approximately 1,000 c.c. of amniotic fluid which is exchanging water at the rate of approximately 350 c.c. per hour. This astonishingly rapid rate of replacement of the water of the human amniotic fluid, like that of the guinea pig, is at variance with the concept that the amniotic fluid is a relatively stagnant body fluid.

### Summary

The rate of passage of water and sodium from the maternal circulation to the amniotic fluid has been measured with heavy water and radioactive sodium as the tracer substances. The water of the fluid is completely replaced on the average once every 2.9 hours; this considerable rate of turnover is at variance with the concept that the amniotic fluid is stagnant. The rate of transfer of water is about five times more rapid than that of sodium.

The heavy water for these experiments was purchased from a grant made by the Abbott Laboratories.

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## **AN INVESTIGATION INTO THE INCIDENCE OF ABORTION IN BALTIMORE**

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**T**O DETERMINE the incidence of abortion in the general population a number of studies have been made in the United States, mainly in large cities. A variety of methods have been used, and great caution must be exercised in interpreting the data. One method employed by several investigators is to determine the number of abortions among the previous pregnancies of a series of obstetric patients, seen at the office or dispensary or admitted to a hospital. This method has the great advantage that questions as to the number and outcome of previous pregnancies are generally accepted as a routine part of the examination, and that there is usually good rapport between the patient and the physician in whom she has a high degree of confidence. To duplicate these conditions is often difficult in other types of studies. The outstanding deficiency of all obstetric series is that no pregnancy will be included unless it is followed by another which brings the case into the investigation. If abortions tend to occur more frequently among last pregnancies they will be underrepresented in the material. In addition, an obstetric series based upon the records of a single physician or a single hospital may be biased by the special professional interests of the doctor or the admission policies of the hospital.

The present paper is based on the case histories of all patients admitted to the Department of Obstetrics of the Johns Hopkins Hospital in Baltimore from 1937 to 1946 who had been pregnant at least once before.

The number of plurigravidas during the ten-year period was 10,397, and the aggregate number of their previous pregnancies 30,133 or 2.9 per patient. Of these 30,133 previous pregnancies 25,009, or 83.0 per cent, had produced a viable birth and 5,124, or 17.0 per cent, had ended in abortion. Unfortunately, it is not possible to say on the basis of the available data how many of these abortions were unintentional and how many were induced.

Of the 10,397 plurigravidas admitted to the service, 9,130, or 87.8 per cent, terminated their current pregnancy with a viable birth and 1,267, or 12.2 per cent, with an abortion. The greater part of these current abortions were probably unintentional, but an unknown number had been illegally initiated prior to admission, and a few were therapeutic. The 9,130 parturient women reported 25,558 previous pregnancies with 4,102, or 16.0 per cent, ending in abortion. On the other hand, the 1,267 aborting women had had 4,575 previous pregnancies, and 1,022, or 22.3 per cent, of these had ended in abortion. The abortion ratio is markedly higher among the previous pregnancies of aborting women than among the previous pregnancies of those who produced a viable birth. This relationship has also been observed by others. Abortions are underrepresented

among the current pregnancies terminated in the hospital. This makes the abortion ratio appear a little lower among the previous pregnancies of these patients than it actually is in the population from which they are drawn. Statistical methods have been devised to correct this bias. With the present material, however, the effect of the correction is so slight that it does not seem worth while to introduce it.

The total group of 10,397 patients can be broken down by color and pay status into three distinct components: 1,985 private patients, all of whom were white; 4,041 white ward patients; and 4,371 Negro ward patients. The aggregate numbers of previous pregnancies and the numbers and percentages of abortions in the three groups are presented in Table I, showing separately the findings for parturient and aborting women.

TABLE I. NUMBER OF WOMEN, OF PREVIOUS PREGNANCIES, AND OF ABORTIONS AND PER CENT OF PREGNANCIES ENDING IN ABORTION, BY COLOR AND PAY STATUS AND OUTCOME OF CURRENT PREGNANCY

COLOR AND PAY STATUS	OUTCOME OF CURRENT PREGNANCY	NUMBER OF WOMEN	NUMBER OF PREGNANCIES	NUMBER OF ABORTIONS	PER CENT ABORTIONS
Private (White)	viable birth	1,779	2,734	647	23.7
	abortion	206	425	146	34.4
		1,985	3,159	793	25.1
White ward	viable birth	3,518	9,816	1,395	14.2
	abortion	523	2,036	432	21.2
		4,041	11,852	1,827	15.4
Negro ward	viable birth	3,833	13,008	2,060	15.8
	abortion	538	2,114	444	21.0
		4,371	15,122	2,504	16.6

The findings of the present study are in line with the results of earlier investigations.<sup>1, 3</sup> In view of the difference in method it is doubtful how comparable they are with Anna Rochester's figures for Baltimore.<sup>2</sup> Her data were based upon a citywide sample of births in 1915, and the reported ratio of previous pregnancies ending in abortion was 7.5 per cent for white and 11.3 per cent for Negro women.

TABLE II. PER CENT OF PREVIOUS PREGNANCIES ENDING IN ABORTION BY COLOR AND PAY STATUS AND NUMBER OF PREVIOUS PREGNANCIES PER WOMAN

PREVIOUS PREGNANCIES	PRIVATE (WHITE)	WHITE WARD	NEGRO WARD
One	17.1	13.0	22.7
Two	26.9	15.1	19.2
Three	30.9	15.3	20.3
Four	34.6	16.0	21.1
Five	36.8	15.7	16.2
Six	41.7	15.7	13.8
Seven or more	41.5	16.2	13.5

Table II presents abortion ratios for the three color and pay status groups by the number of previous pregnancies per woman. A very striking pattern emerges. Among the private patients the abortion ratio increases steeply with increasing number of previous pregnancies. In the white ward group no clear trend is apparent. Among the Negroes the abortion ratio is seen to decrease with increasing number of pregnancies.

The high abortion ratio observed among the private patients and the pattern by pregnancy order seen in this group suggest a population which controls its reproduction mainly by contraceptive methods, but without achieving complete success. In such a group many women will resort to induced abortion if a conception has occurred in excess of the number planned or at a time when it was not wanted. Those, on the other hand, who have had one or more unintentional abortions continue their efforts to have the number of babies they originally intended. Both mechanisms tend to produce a high abortion ratio which increases with the number of previous pregnancies.

The pattern among the Negroes, which is just the opposite from that seen in the private group, is an artefact resulting from the admission policies of the hospital. During the years covered by the present study, the number of hospital beds on the Negro ward has never been sufficient to accommodate all patients seeking admission and preference has been given—among others—to two categories: To those who had produced no previous viable birth and to those who had had very many. The effect of this policy has been to increase the abortion ratio among the secundigravidae and to reduce it among the multigravidae of the hospital material on which the study is based.

### Summary

1. Report is made on 30,133 previous pregnancies of 10,397 patients on an obstetric service.
2. Of these pregnancies 5,124, or 17.0 per cent, ended in abortion.
3. The abortion ratio was higher among the previous pregnancies of aborting than of parturient women.
4. The abortion ratio was 25.1 per cent for private patients (white), 15.4 per cent for white ward patients, and 16.6 per cent for Negro patients.
5. With increasing number of previous pregnancies the abortion ratio increased for private patients, decreased for Negro patients, with no clear trend for white ward patients.

I want to thank Dr. Nicholson J. Eastman for his permission to use these records, and Mr. L. Omar Huesman for his aid in tabulating the data.

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## Rh SENSITIZATION IN A PRIMIPARA CAUSED BY INTRAMUSCULAR INJECTION OF HUMAN SERUM RESULTING IN FATAL ERYTHROBLASTOSIS

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IT IS now generally recognized that transfusions, or even intramuscular injections of Rh-positive blood are far more potent in sensitizing Rh-negative individuals than is pregnancy with Rh-positive fetuses. Thus, while only one of about 25 Rh-negative women bearing Rh-positive babies becomes sensitized to the Rh factor, fully one-half of such individuals can be sensitized by injections of Rh-positive blood.<sup>1</sup> This difference is readily explained by the difference in quantity of antigen injected. On the other hand, it has been generally believed up to now that such sensitization could not result from the injection of serum or plasma, which is presumably free of red cells.

The purpose of this report is to present possibly the first case which demonstrates that such sensitization can occur after intramuscular injection of serum, causing fatal erythroblastosis even in a firstborn infant.

### Case Report

Mrs. B. G., aged 24 years, was first seen by one of us (J.T.W.) on Jan. 30, 1947, in the fifth week of her pregnancy. Routine antenatal Rh test revealed that she was Rh negative, her husband Rh positive. Careful inquiry elicited no history of her having had either transfusions or injections of whole blood during infancy, childhood, or adult life. However, in discussing the matter with her father, who is a physician, he recalled that she had once had an intramuscular injection of pooled adult serum as a prophylactic measure against poliomyelitis. This had been given in October, 1931, when she was 8 years of age. The serum had been collected, prepared, and given by our own serologist as follows:

Twenty cubic centimeters of whole blood were drawn from each of six adult donors. Each specimen was "Wassermannized"; they were then centrifuged individually to obtain the serums which were pooled. The pooled serum was diluted with normal saline to make a solution of 40 per cent serum. Ten cubic centimeters of this solution were injected intramuscularly into each buttock.

Though it has been thought in the past that serum alone would not cause the production of Rh antibodies in Rh-negative individuals, she was nevertheless submitted to a more complete study which showed the following:

Blood of	Group	M-N Type	Rh-Hr Type*	
Prospective father	O	M	Rh <sub>2</sub> rh	R <sup>2</sup> r, R <sup>2</sup> R <sup>0</sup> or r"R <sup>0</sup>
Prospective mother	A <sub>1</sub>	MN	rh	rr

\*The M-N types are not important clinically, but are included for the sake of completeness. For a detailed description of the Rh-Hr types and their heredity see publications of Wiener.<sup>2, 3</sup>

These results confirmed the original report that the mother is Rh negative and her husband Rh positive. Moreover, the husband was *presumably* heterozygous for the Rh factor as determined by tests with anti-Hr" serum.\*

These tests were first made in the seventh week of pregnancy. At that time it was already possible to demonstrate the presence of Rh antibodies in the prospective mother's serum. She was accordingly studied at intervals during her pregnancy with results recorded in Table I. Despite the administration of typhoid and pertussis vaccine for purposes of counter-immunization, the antibody titer rose as shown in Table I.

TABLE I. RESULTS OF RH ANTIBODY TITRATION DURING PREGNANCY

TIME OF TEST	ANTIBODY TITER (UNITS) BY THE METHOD OF			
	AGGLUTINATION (IN SALINE MEDIA)	BLOCKING (IN SALINE MEDIA)	CONGLOUTINATION (IN PLASMA)	CONGLOUTINATION (IN ALBUMIN- PLASMA)
7 weeks	0		1½	4
17 weeks	0		6	11
23 weeks	0		3	12
27 weeks	0		3½	16
31 weeks	0	60		1,400

Otherwise her pregnancy progressed entirely normally except for an anemia which responded even better than usual to iron therapy, until the thirty-second week. At this time the obstetrician was suddenly presented with the urgent problem of terminating the pregnancy at once in the interests of the baby because of a sudden extreme increase in the titer of the Rh antibodies in the maternal serum, and the serious probability that this might well be the only chance this patient might ever have of bearing a live baby. Clinically, the fetus appeared larger than would ordinarily be expected at this period of gestation, arousing the suspicion that it might already be suffering from fetal hydrops. X-ray showed only one fetus in utero and from the size of the bones, it was felt that it was a large fetus rather than an hydropic one. The vertex appeared to be somewhat extended. Vaginal examination showed the cervix to be long, very firm, and tightly closed. The presenting part was well down in the pelvic inlet, and on the right an orbital ridge and eye could be felt, making it essentially a brow presentation. Since termination of the pregnancy was solely in the interests of the baby, and since even the time consumed in a long labor might further damage the baby, with conditions so adverse to induction from below, cesarean section was performed under fractional spinal anesthesia without further delay. The baby was a living male which cried vigorously immediately after delivery and weighed 5 pounds, 5 ounces. Exsanguination transfusion was begun on the baby within fifteen minutes of delivery. The mother's postpartum course was uneventful.

In so far as the infant was concerned, it was planned to proceed with exsanguination transfusion at once without waiting for laboratory determinations or any other clinical data, because the antenatal serologic tests indicated that we were dealing with a severely affected infant who would have been stillborn had the pregnancy been allowed to proceed any further. Before the cesarean operation, therefore, 500 c.c. of blood were drawn from a Group A type rh donor and mixed with 60 c.c. of citrate solution in preparation for the transfusion. Two-fifths of the plasma was removed and replaced with saline solution.†

At birth no apparent abnormalities were noted except for pallor of the baby and marked icterus of the umbilical cord. The hemoglobin concentration, as subsequently reported, was only 44 per cent (6.4 Gm.) and the red blood cell count 1.21 million per cu. mm.

\*The prospective father was Hr" positive as determined with serum kindly provided by Dr. A. E. Mourant.

†We have found that these babies do best if fresh blood rather than bank blood is used for the exchange transfusion. Since the prospective mother belonged to Group A and the father to Group O, we knew that a Group A donor would be compatible even before the baby was born.\* After experience with this and other similar cases we now use as much as 1,000 c.c. instead of 500 c.c. for replacement transfusion in such severely affected infants.† This has proved more effective than the replacement of part of the donor's plasma with saline.

The baby was given oxygen. His tone and cry were good. As already mentioned, within fifteen minutes of delivery an exchange transfusion was started. During a two-hour period 380 c.c. of blood were injected into the left saphenous vein at the ankle, while 345 c.c. of blood were withdrawn from the right radial artery. The infant withstood the procedure well and seemed in good condition at its termination. He was then transferred to the nursery where he received newborn care and was placed in the incubator with continuous oxygen. The baby did not appear to be jaundiced. The liver and spleen were not palpable, and the hemoglobin concentration was now 80 per cent (11.6 grams).

Three and one-half hours after transfusion, definite jaundice was noted. The liver and spleen were palpable two and one-half fingerbreadths below the costal margin. The baby continued to be lively and had a good cry. The hemoglobin concentration had risen to 85 per cent (12.3 Gm.) by the time the baby was eight hours old. Physical examination was essentially as noted above except that the respirations were somewhat shallow and rapid. Because of the appearance of rapidly increasing jaundice which, in similar cases, we had previously found to indicate impending nuclear jaundice, an attempt was made to prevent intravascular conglutination of the remaining 15 per cent of the infant's blood cells, which had not been removed by the exchange transfusion, by instituting a continuous infusion of 15 c.c. of normal saline per hour. In addition 10 c.c. of blood were given each hour for five hours. This was effected through a "cutdown" in the right ankle vein.

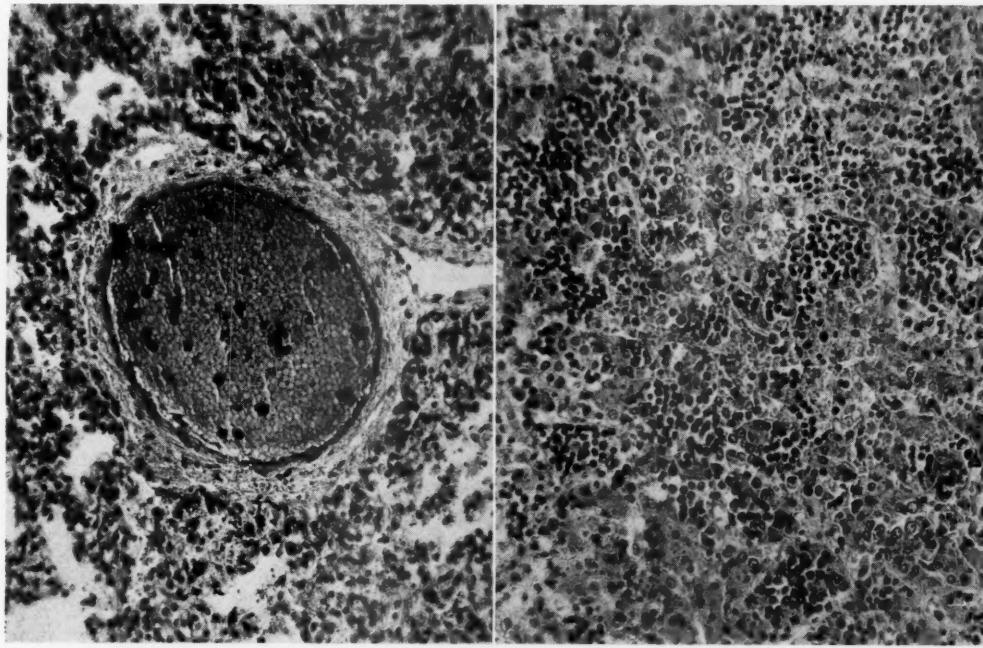


Fig. 1.—(A) Section of lung showing small blood vessel plugged with erythrocytes. (B) Section of liver showing multiple islands of hematopoiesis.

The baby voided a scanty amount of deep yellow urine. He retained three feedings in eighteen hours after birth which all feedings were refused.

Physical examination twenty-four hours after birth showed the jaundice to be deeper with a reddish tinge. The hemoglobin concentration at that time was 100 per cent (14.5 grams). There was some edema of the thighs. The heart and lungs were normal. The

spleen was smaller and the liver was not felt. The baby was apparently doing well, when about one hour later he began having respiratory difficulties. The intermittent periods of apnea and cyanosis were treated with carbogen, coramine, and artificial respiration. A small amount of blood was noted coming from the right nostril.

Four hours later the infusion was discontinued, after a total volume of 180 c.c. of saline had been administered. The baby's extremities and eyelids were edematous at this time. Shortly after this (one-half hour) the infant was pronounced dead.

Subsequent tests confirmed the prediction that the baby was Rh positive (his complete classification was Group A, Type M, Type Rh<sub>2</sub>). As a matter of fact, the blood cells failed to clump in anti-Rh<sub>2</sub> serum, but this was due to complete coating of the infant's cells by the maternal Rh-blocking antibodies as proved by the anti-globulin technique of Coombs and associates.<sup>6</sup> In addition, the cord serum contained free univalent Rh-antibodies of a titer of 400 units by the albumin-plasma technique.<sup>7</sup> The icterus index of the cord serum was 50 units by the acetone method, and the last sample obtained from the radial artery at the exchange transfusion had an icterus index of 38 units and Rh-antibody titer of 180 units. The fact that the icterus index and antibody titer did not decrease by 87 per cent in proportion to the replacement of red cells, can be explained, as pointed out in previous papers,<sup>8</sup> by diffusion of bile and antibodies from the tissues into the circulation during the transfusion. In view of these extreme serologic findings, a fatal outcome was to be expected in spite of the exchange transfusion.<sup>8</sup>

The most significant gross postmortem findings were the large size of the placenta (760 Gm. or about one-third the weight of the infant), edema of the skin, generalized passive congestion, hepatosplenomegaly and edema of the brain with nuclear jaundice. The significant microscopic findings were disorganization of the liver cords with numerous large islands of hematopoiesis and plugging of the smaller blood vessels in the lungs by masses of red cells together with some erythroblasts.

Subsequently blood was obtained from the parents of the father and classified with the following results:

<i>Blood of</i>	<i>Group</i>	<i>M-N Type</i>	<i>Rh-Hr Type</i>	<i>Phenotype</i>	<i>Genotype</i>
Paternal grandfather	O	M	Rh <sub>1</sub> Rh <sub>2</sub>	R <sup>1</sup> R <sup>2</sup> , r'R <sup>2</sup> or R <sup>1</sup> r'	
Paternal grandmother	O	MN	rh		rr

These findings proved that the father of the patient, previously found to belong to type Rh<sub>2</sub>rh, is, with certainty, heterozygous. Repeat Rh-antibody titrations on the maternal serum two months post partum still showed a titer of about 1,000 units. Regarding future pregnancies, therefore, the following prediction can be made. There is an equal chance of future infants being either Rh positive or Rh negative. If Rh negative, naturally the infant will not be erythroblastotic; if Rh positive in view of the high maternal Rh-antibody titer it will be severely affected and so early in pregnancy that a stillbirth will be inevitable. Experience in similar cases indicates that it is unlikely that the Rh-antibody titer in this mother's serum will drop low enough during her childbearing period to enable her to have a viable Rh-positive fetus. Thus in future pregnancies we would be dealing with an all-or-none proposition with the outcome depending entirely on the Rh type of the fetus.

### Summary and Conclusions

A case is reported in which a young primigravida is presumed to have been sensitized to the Rh factor by an injection of pooled human serum, given as a prophylactic measure against poliomyelitis during childhood, and in whose baby fatal erythroblastosis developed.

Accordingly, we should like to emphasize to clinicians that the injection of serum or plasma into Rh-negative women may create Rh sensitization. The hazard of such injections is at times as great as that accompanying the injection of Rh-positive whole blood, and may deprive even primiparas of the opportunity of having normal babies. Therefore, it is urgently recommended that in taking obstetric histories careful inquiry be made into whether or not

such injections have been received by the patient. It is likewise recommended that all physicians exercise utmost care and discretion in the use of these substances.

Since the preparation of this report, our attention has been called by personal inquiry from a California physician, to a second case of erythroblastosis in a firstborn baby whose mother may have been sensitized by injection of pooled serum as a prophylactic measure against poliomyelitis.

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80 HANSON PLACE

## SULFADIAZINE CONCENTRATION IN THE BLOOD AND LOCHIA

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THIS study was undertaken to determine the amount of the sulfonamides excreted from the postpartum uterus and its relation to the blood concentration. The recent use of chemotherapy justifies this report. These patients were afebrile and the use of the sulfonamide was academic.

In this series of twenty-five patients, all but three were primiparas; two were gravida ii and one was gravida iii. Their prenatal and labor courses were normal. Each primipara was delivered by outlet forceps under pudendal block with mediolateral episiotomy.

### Procedure

Sulfadiazine was started within twelve hours after delivery. The routine consisted of 60 grains initially and 15 grains every four hours, with equal amounts of sodium bicarbonate. Lochia was collected after twenty-four and forty-eight hours, and after seven days, by means of a contraceptive vaginal diaphragm. This diaphragm was inserted and removed with sterile technique.

It was found that the diaphragm has to be inserted four to five hours prior to the collection of the twenty-four and forty-eight specimens in order to obtain the necessary amount (8 to 10 c.c.) of lochia. Upon the removal of the diaphragm and its contents, blood was drawn from the cubital vein. Both specimens were collected in oxalated bottles. The seven-day lochia was collected by a diaphragm placed ten to twelve hours before, since the output at this postpartum period was minimal. This seven-day specimen was of particular interest because the lochia contained little blood, with an abundance of shreds and debris from the uterus.

All contents were kept refrigerated and taken to the Institute within twelve hours. The sulfadiazine levels were determined by the same technician, using the Bratton-Marshall Photelometer technique.

Patients were ambulatory after the first postpartum day, save during the period of lochial collection. Only one tablet of Ergotrate, grain  $\frac{1}{320}$ , was given to each patient post delivery.

The sulfa concentrations in the blood were extremely variable for all groups, remaining proportionately similar in each case. Thus patient No. 2 revealed a level of 5.87 mg. per cent at the end of twenty-four hours, and 7.5 mg. per cent at the end of forty-eight hours. On the other hand, patient No. 14 had a blood level of 15.9 mg. per cent at the end of twenty-four hours and 14.2 mg. per cent at the end of forty-eight hours. Lochial concentrations behaved in a similar manner, though less in amount. Thus, in patient No. 2, the sulfonamide blood concentration at the end of twenty-four hours was 5.97 mg. per cent, while the lochial concentration was 4.74 mg. per cent. Again, patient No. 14 revealed a blood concentration of 18.9 mg. per cent at the end of twenty-four hours and a lochial concentration of 15.7 mg. per cent. Thus, if the concentration of the sulfadiazine was

high in the blood, we could expect high concentration in the lochia. This is true whether we study the twenty-four hour or the seven-day specimen (Table I).

There are paradoxical levels noted in the 48-hour specimen for patients No. 2, No. 3, No. 13, and No. 14, as well as in the seven-day specimen of patients No. 19, No. 21, and No. 25. In these, the diaphragm had to be retained for longer periods than the time allotted for the medication, because the lochia collected for the previous four to five hours and ten to twelve hours, respectively, was not sufficient for analysis. It would seem to indicate that a fairly rapid loss of sulfadiazine occurs in the blood stream, and, despite their ambulatory state, some patients still discharge small amounts of lochia.

The character of the lochia was no different than in the nonmedicated patients, although the odor tended to be "sharper." There were no complications in any of these patients, and all were discharged on the eighth postpartum day.

TABLE I

PATIENT	24 HOURS		48 HOURS		7TH DAY	
	BLOOD (MG. PER CENT)	LOCHIA (MG. PER CENT)	BLOOD (MG. PER CENT)	LOCHIA (MG. PER CENT)	BLOOD (MG. PER CENT)	LOCHIA (MG. PER CENT)
1	12.19	9.45		Specimen was lost		
2	5.97	4.74	7.5*	9.0		
3	15.0	8.59	16.23*	27.23		
4	12.64	10.47		Specimen lost		
5	7.38	4.47	8.37	5.43		
6	9.7	8.82	8.37	7.0		
7	11.4	10.3	10.39	9.0		
8	6.31	4.17	7.2	5.15		
9	7.3	4.0	7.6	6.0		
10	11.38	7.65	7.95	6.85		
11	8.37	7.6	7.5	6.2		
12	10.3	10.3	8.9	5.1		
13	5.7	3.5	4.4*	4.6		
14	18.9	15.7	15.5*	17.2		
15	15.9	14.2	11.7	10.9		
16					6.8	4.9
17					8.3	5.5
18					7.3	6.0
19					5.9*	6.7
20					8.0	7.5
21					10.9*	11.4
22					7.5	6.9
23					3.0*	5.6
24					5.4	4.0
25					12.9*	15.7

\*See Discussion.

### Summary

1. The sulfonamide concentration of the lochia paralleled the blood concentration in each instance.
2. The sulfadiazine routine of 60 grains initially and 15 grains every four hours results in extremely variable blood and lochial concentrations.
3. Ambulatory patients do not always reveal an increase in the amount of lochia.
4. The lochial odor of these patients tended to be "sharper" than that of those nonmedicated.

## A FULL-TERM LIVE TUBAL PREGNANCY

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**T**HIS 32-year-old, married, Negro para vii, gravida viii was admitted to Freedmen's Hospital at 3:55 P.M. July 18, 1947, on the request of her family physician, who had followed her prenatal course from approximately the third month in the Antepartum Clinic of a neighboring state. After following her labor in the home for a period of fourteen hours without progress, he sensed a complication necessitating hospitalization. On entrance, she showed evidence of delirium, exhaustion, and dehydration.

Her prenatal course was significant in that she complained throughout of abdominal pain. Interrogation localized this pain more to the left lower quadrant, gradually moving to the upper quadrant as the pregnancy progressed. She was referred to the Consultation Clinic during her sixth month for examination and x-ray. The consultant did not recognize any abnormality. Her last menses were Oct. 21, 1946, and her expected date of confinement July 28, 1947, ten days later than her date of admission.

In her delirious state, the patient was complaining intermittently of lower abdominal pain not coincidental with uterine contraction. The globular abdomen was unduly prominent, giving one the impression of a giant child, multiple pregnancy, or polyhydramnios. Palpation of the abdomen was quite painful to the patient and revealed a single large fetus in the transverse plane with a large prominent head in the right lower quadrant at the pelvic brim. Fetal movements were dubious and heart sounds could not be elicited. Rectal examination revealed a parous, nondilated, only slightly softened cervix. Considering prolonged labor with exhaustion due to fetopelvic disproportion from a monstrosity or giant child as a likely diagnosis, a flat plate of the abdomen was taken.

A wet reading of the plate revealed a single uterine pregnancy with the body in a transverse lie possessed of an unusually large head measuring approximately 15.2 cm. in its occipitofrontal diameter. A final reading, not available preoperatively, stated that the apparent enlargement of the head was caused by undue distortion. Furthermore, the outline of the uterus could not be demonstrated but the pelvic inlet appeared relatively small.

Blood pressure was 130/80, pulse rate 120, temperature 100.6° F., and respiration 26.

Clinical impressions at this time were as follows: Fetopelvic disproportion; giant or hydrocephalic fetus; transverse presentation with no cervical dilatation; maternal exhaustion with low-grade fever following fourteen hours of labor without obvious progress. Consensus of opinion now favored abdominal delivery, if the patient's general condition could be sufficiently improved following the administration of fluids, blood, sedation and antibiotics. Three hours later she was considered a fair risk for cesarean section under Nembutal and local anesthesia.

When the abdomen had been opened in the midline, there presented a smooth, congested surface, below which the fetal parts could be palpated with ease. Suspicions as to the nature of this sac were confirmed when the bladder flap could not be identified prior to performance of a low segment operation. The uterus, found to be only slightly enlarged and softened, was pushed forward and downward by this abdominal mass. The possibility of an extrauterine pregnancy now became a fact.

In the process of separating the mass from the inferior surface of the liver, the parietal peritoneum, and contiguous loops of intestines to which it was firmly adherent, the wall

was inadvertently ruptured, releasing under pressure a moderate amount of dark brown amniotic fluid. Suction was applied and the opening was extended to deliver a large, normally developed, live, male fetus weighing 9 pounds, 5½ ounces, and measuring 51.25 cm. in length. The infant breathed spontaneously and its condition remained good throughout the hospital period.

The placenta was attached to the inferior and inner aspect of the sac wall and was the site of a moderate amount of bleeding which made its immediate removal necessary. Closer inspection of this gestation sac revealed it to be the left tube with the isthmal portion readily identifiable. The ampullary and infundibular portions were widely dilated. The operation consisted further in removal of the left tube, peritonealization of rough surfaces, sprinkling of 5 Gm. of sulfanilamide powder over the operative site, and a quick abdominal closure in layers as the patient's condition was never better than fair. Her postoperative course was uneventful. Both mother and infant were discharged in good condition on the eleventh day after operation.

#### Pathological Report

*Macroscopic.*—"Received partially immersed in formalin fixative are two specimens. One is a bi-lobed placenta, with a 57 cm. length of umbilical cord attached to the larger lobe, which measures 13 by 9 by 6 cm. in maximum diameters. There is an isthmus measuring 5 by 5 by 2.5 cm. connecting this to the other lobe which measures 12 by 9 by 8 cm. The other specimen is a wrinkled, partially translucent, and pouch-like membrane varying from 1 mm. to 1 cm. in thickness. The thinner part presents relatively smooth inner and outer surfaces and areas where it can be split into two layers; the thicker part of the membrane has a relatively smooth outer surface but the inner surface is roughened by hemorrhagic and grayish strands. This thicker part of the specimen has an area of approximately 17 by 9 cm., while that of the thinner part is about 17 by 20 cm. No ovarian tissue or tubal tissue is recognized as such, except for the lumen of the attached isthmal portion of the tube opening into the cavity of this sac-like structure."



Fig. 1

*Microscopic.*—"Section 1 reveals cross-section of the isthmus of the fallopian tube with a wall of hypertrophied smooth muscle fibers, abundant vascularization, and an increased amount of fibrous tissue." (Fig. 1.)

"Section 2 is from the thicker part of the fetal sac having a relatively smooth surface covered by fibrin, a wall consisting of smooth muscle fibers and connective tissue, and a lining which includes placental tissue and exudate showing varying degrees of necrosis and lysis." (Fig. 2.)

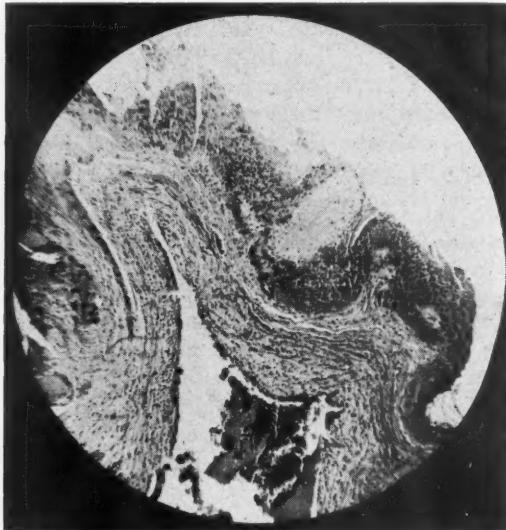


Fig. 2.



Fig. 3.

"Section 3 is from the thinner part of the saclike structure, the inner surface of which presents columnar epithelium (tubal) overlying decidual cells, fibrinous exudate, necrotic tissue, and a chorionic villus." (Fig. 3.)

*Impression.*—"Tubal pregnancy at term."

### Comment

The literature is replete with the possible termination of tubal pregnancy but we were not able to find one reference to the salvaging of a live full-term fetus from an unruptured uterine tube.

Lichtenstein<sup>1</sup> called attention to the fact that, when the placenta develops toward the mesosalpinx, the pregnancy is more likely to continue. In 90 per cent of advanced tubal pregnancies, this "basiotrope" implantation is found.

To this postulation, we offer as an additional possibility, a luminal implantation site into the connective tissue stroma of the numerous and elongated mucosal folds in the ampillary portion of the tube, permitting little or no encroachment upon the tubal wall by the trophoblastic villi—a phenomenon not possible in a mural or luminomural implantation site.

Appreciation is acknowledged for the cooperation of the Pathology Department of Howard University Medical School.

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## PREGNANCY COMPLICATED BY SUBARACHNOID HEMORRHAGE

### A Report of Three Cases

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SUBARACHNOID hemorrhage has been established as a definite, relatively common clinical entity in the past sixty years. It rarely occurs, however, as a complication of pregnancy, labor, or the puerperium. Moskowitz and Schneider, in 1938, reported three cases occurring during labor. They found thirteen cases reported up to that date. A recent search of the literature revealed only four additional occurrences: one reported in 1938 by Pancot and Galle, secondary to an intracerebral accident due to syphilis; and three reported by T. Dahle in 1946, in which toxemia of pregnancy was considered the causative factor.

In the general consideration of subarachnoid hemorrhage, aside from its occurrence as a complication of pregnancy, a variety of diseases and conditions has been suggested as etiologic factors. Infections such as influenza, typhoid, smallpox, and syphilis; toxic conditions including alcoholism, lead poisoning, and toxemias of pregnancy; and vascular lesions like arteriosclerosis and aneurysms have all been considered. The latter have been found most frequently. Two types of subarachnoid hemorrhage are distinguished: primary and secondary. In the first, the bleeding is into the subarachnoid space from a ruptured adjacent artery. This type is characterized by headache, delayed loss of consciousness, and late signs of paralysis. In the second type the bleeding is due to extension of intracerebral hemorrhage into the subarachnoid space, and is characterized by early signs of paralysis and rapid loss of consciousness. The latter occurs more often in the older age groups, and is usually on an arteriosclerotic basis. In the primary type the younger age groups are more commonly affected, and the cause is thought to be a rupture of a small "berry" type congenital aneurysm. Such aneurysms are frequently found at routine autopsies in which the incidence is reported to be 0.3 to 1.0 per cent. Congenital aneurysms result from a local weakness or defect in the media of the cerebral arteries and occur at the points of bifurcation in the region of the Circle of Willis where the vessels are essentially suspended in fluid with little external support. These vessels may rupture easily under the impact of trauma from emotional strain, increased systolic pressure, or physical exertion.

In the initial phase of the accident the striking symptoms of headache, vomiting, bradycardia, followed by stupor and coma, manifest themselves. If the patient does not succumb shortly after the accident the condition progresses with signs of meningeal irritation such as pain in the head, rigidity of the neck, a positive Kernig's sign, leucocytosis and fever. The pathognomonic sign of subarachnoid hemorrhage is the finding of bloody spinal fluid under increased pressure.

### Case Reports

CASE 1.—I. R. T., a 26-year-old Negro para 0, gravida ii, in her eighth month of gestation, was admitted to the hospital on Sept. 10, 1946, with painless vaginal bleeding of about ten hours' duration. At the time of the onset of the vaginal bleeding she complained of nausea, vomiting, and severe frontal and occipital headache, throbbing in character. The past history was essentially negative except for a spontaneous three-month miscarriage in 1945. Her blood pressure was essentially negative. The uterus was enlarged to almost the size of a term pregnancy, and the fetal heart tones were heard. A catheterized urine specimen revealed a two plus albumin and hyaline casts. An x-ray examination of the abdomen with air insufflation of the bladder demonstrated a shadow suggestive of a low implantation of the placenta on the left posterior aspect of the uterus. A tentative diagnosis of partial placenta previa and toxemia of pregnancy was made, and it was decided to deliver the patient

by cesarean section. Lumbar puncture for spinal anesthesia showed a uniformly bloody spinal fluid, but its significance was overlooked. A low cervical section was done and a premature viable male infant delivered. For three days postoperatively she ran a temperature of 100.5° F. She continued to complain of headache, but this was considered to be due to spinal anesthesia. On Sept. 16, 1946, her temperature rose to 102° F. She complained of severe headache and nuchal rigidity, but there was no nausea or vomiting. Examination on that date revealed no eye signs or pathologic reflexes, but definite evidence of meningeal irritation developed gradually in the form of a fine nystagmus, marked nuchal rigidity, absent upper reflexes, depressed lower reflexes, and a positive Kernig's sign. A lumbar puncture on Sept. 20, 1946, revealed a grossly bloody fluid with an initial pressure of only 190 mm. of water and a four plus Pandy. The headache and nuchal rigidity gradually subsided. Spinal puncture on September 21 and September 23 demonstrated a gradual return to normal with the fluid on the latter date showing a xanthochromic color and only an occasional red blood cell and a one plus Pandy. The patient had a clear sensorium and was discharged from the hospital on Sept. 27, 1946, in good condition. The laboratory findings during her stay at the hospital were not remarkable. The urine which on admission had shown a two plus albumin became negative. On September 16 the white count rose to 10,650, but at other times was within normal range. Blood chemistry and serology were normal. A spinal fluid culture on September 21 showed no growth.

In this case the accident, in all probability, occurred prior to her cesarean section as evidenced by her symptoms on admission and the bloody spinal fluid obtained at that time. It was overlooked due to the existence of a toxemia.

CASE 2.—D. R., a 26-year-old white multipara, was admitted to the hospital on Nov. 20, 1946, in her thirty-fourth week of gestation, with a complaint of severe headache. Nine hours prior to admission the patient bent over and suddenly experienced a terrific pounding in the frontal region which subsequently became generalized and progressively more severe. She felt faint, did not lose consciousness, and within one and one-half hours developed marked nausea and projectile vomiting. Her family and past history was negative. She had had one child and one abortion. She did not appear acutely ill. The blood pressure on admission was 110/70; the pulse rate 66. Her pupils reacted to light and accommodation and the right fundus showed evidence of papilledema. There was moderate nuchal rigidity, but no pathologic reflexes were present. A spinal puncture revealed a uniformly bloody fluid with an initial pressure of 280 mm. of water which dropped to 180 mm. upon slow withdrawal of the fluid. She was maintained at absolute bed rest, but in spite of that she apparently had a second episode of bleeding with an exacerbation of the headache. Examination at this time revealed well-established bilateral papilledema and absent patellar reflexes. Spinal puncture showed a xanthochromic fluid with pressures identical with those of the tap on admission. During the next several days, except for dizziness on movement of her head, the patient showed signs of improvement. She was allowed to be up on December 12, and the following day was found sprawled unconscious on the floor. Her breathing was stertorous. She vomited and urinated involuntarily. All superficial and deep reflexes were hyperactive; and bilateral positive Babinski and ankle clonus were present. She gradually became excited and incoherent. Her temperature for the first time rose to 100° F. A spinal puncture the following day again showed a grossly bloody fluid with an initial pressure of 560 mm. of water which was reduced to 260 mm. by withdrawal of fluid. On December 15 the patient appeared to be moribund. In view of the fact that the baby was viable, and that the additional trauma of labor was undesirable, it was decided to terminate the pregnancy by section before term. The lumbar puncture for spinal anesthesia still revealed a bloody fluid and an initial pressure of 450 mm. of water. A classical section was done, and a 7-pound viable female infant delivered. The patient regained consciousness promptly after the operation, and her improvement was uninterrupted and progressive. In a period of seven days spinal fluid pressure dropped from 600 mm. to 300 mm. of water. She showed evidence of encephalopathy simulating schizophrenia. But within a week she manifested marked improvement, showed a return of considerable alertness, and was discharged from the hospital on Jan. 7, 1947, in good condition.

The laboratory findings were at no time remarkable. She had a moderate leucocytosis ranging from 9,100 to 11,550, but red counts, bleeding, and clotting times, prothrombin indices, blood chemistries, and serologies were all normal. Spinal fluid chemistries due to the admixture of blood were not reliable, and spinal fluid cultures, which revealed nothing on direct smear, showed a slight growth of gram positive cocci believed to be a contaminant.

While the diagnosis in this case was relatively easy and definite, the treatment and management were uncertain. The main problem was the selection of the propitious time for the termination of pregnancy in view of the danger of precipitating another and perhaps fatal hemorrhage. Her apparently moribund state, however, forced the issue with, fortunately, a satisfactory outcome.

CASE 3.—W. W., a 24-year-old white primiparous female, was admitted to the hospital on June 19, 1947, in active labor at term. Examination showed that she was almost ready for delivery. Under general anesthesia a term male infant was delivered with low forceps at 7:30 P.M. Following delivery a tendency toward postpartum bleeding was noted and the patient received an ampule of infundin intramuscularly, an ampule of ergotrate, and a cubic centimeter of pitocin intravenously in the course of some twenty minutes. At 8:15 P.M. she reacted from her anesthesia, became quite restless, and was given  $\frac{1}{4}$  grain morphine. The following day the patient appeared drowsy, but that was attributed to the effect of the anesthesia. On June 21, 1947, she complained of a marked headache. The next day the headache became more severe, and she had a stiffness of her neck with no apparent other signs. A spinal puncture was done and uniformly bloody fluid obtained with an initial pressure of 360 mm. of water, which on withdrawal of the fluid came down to 210 mm. By June 23 her temperature rose to 102° F., she became markedly lethargic, and complained of severe frontal and occipital headache. Examination disclosed marked nuchal rigidity, a positive Babinski, and resistance to straight leg raising, but her pupils and fundi remained normal. The blood pressure was 120/70 and the pulse rate fifty. The following day another spinal puncture again showed a grossly bloody fluid and an initial pressure of 332 mm. of water which was reduced to 162 mm. by withdrawal of fluid. She was treated expectantly with absolute bed rest and became more alert, her headaches gradually subsided, the pulse rate rose to seventy, and her nuchal rigidity and pathologic reflexes disappeared. She was allowed to be up July 2, and was discharged from the hospital the following day with no apparent residual signs. The laboratory findings were not remarkable. She ran a leucocytosis of from 11,100 to 14,050 with 86 per cent polymorphonuclears. Hemoglobins, red counts, blood chemistries, and serology were normal. Spinal fluid examinations were grossly bloody and showed positive Pandys and high cell counts.

This case is of interest in that it exemplifies the dangers inherent in the liberal use of oxytocics, because such drugs may give rise to just enough pressor action to precipitate rupture of a congenital aneurysm with resulting subarachnoid hemorrhage.

### Discussion

The cases here presented are all proved examples of subarachnoid hemorrhage complicating pregnancy, labor, and the puerperium. All occurred in young women of 24 and 26 years of age. Since none showed either early coma or residual paralysis they were probably of the primary variety and most likely secondary to congenital aneurysms of the Circle of Willis. Two of our cases presented similar patterns including normal blood pressures, moderate elevations of temperature, moderate leucocytosis, grossly bloody spinal fluid with markedly increased pressure, and meningeal signs such as nuchal rigidity and pathologic reflexes several days following the original accident. The third case differed from the others in that the blood pressure was moderately elevated and the spinal fluid pressure was not unduly high. In two of our cases, as in those reported by Moskowitz and Schneider, toxemia was not a factor; but in one, as in the three cases reported by T. Dahle from Norway, toxemia may have played a role in the etiology. The diagnosis of subarachnoid hemorrhage complicating pregnancy and delivery may be obscured by other conditions such as shock, anesthesia, and a pre-eclampsia. Dahle and others have emphasized the latter possibility and have pointed out that

without recourse to spinal puncture a mistaken diagnosis may be made. Still another factor which may obscure the diagnosis is delivery under spinal anesthesia, since the manifestations of "spinal headache," nuchal signs, and meningismus are frequently encountered following that type of anesthesia. In spite of the fact that lumbar puncture in the face of an increased intracranial pressure is considered by many as a dangerous procedure, all of these cases were subjected to repeated punctures. Removal of the irritating bloody fluids and lowering of the intracranial pressure apparently served to decrease the meningeal irritation and lessen the lethargy. The taps were done cautiously, the fluid removed slowly; and in the cases with increased pressure, the pressure was decreased by not more than half. The delivery of Case 2 by cesarean section was in accord with the conclusion of Moskowitz and Schneider that when the diagnosis has been established, cesarean section offers the least additional trauma. The emptying of the uterus in this case seems to have been a factor in her recovery. It is quite possible that cesarean section by decreasing abdominal pressure and allowing for stagnation in a dilated splanchnic vascular bed decreases the circulating blood volume, the venous pressure, and hence the intracranial pressure.

### Summary

1. Three cases of proved subarachnoid hemorrhage complicating pregnancy have been reported.
2. All three were apparently of the primary type and probably occurred at the sites of congenital aneurysms of the Circle of Willis.
3. Oxytocics should be used cautiously, particularly in cases with elevated blood pressure, a history of migraine, or any suggestive premonitory signs.
4. The use of repeated spinal puncture to relieve the symptoms of intracranial pressure and the employment of cesarean section to avoid the trauma of labor proved efficacious in the cases reported.
5. Subarachnoid bleeding may occur in milder forms, and be obscured by general anesthesia, shock, toxemia, or symptoms of "spinal headache."
6. The more frequent employment of diagnostic lumbar puncture would obviate those sources of error since the finding of bloody spinal fluid under increased pressure is pathognomonic of subarachnoid hemorrhage.

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## KIDNEY FUNCTION IN THE FETUS

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THE function of the vital systems of the fetus during intrauterine life has been discussed to a very limited extent in our textbooks in the past. This material is neither within the scope of the embryology textbook nor the physiology textbook. The treatment of a premature infant and also an evaluation of its prognosis are based on a knowledge of the physiology of the fetus. Evidences of the onset and extent of activity of the various organs come, for the most part, from indirect findings, but occasionally some direct evidence presents itself. This case is reported because it gives some indication of the quantity of urine excreted during fetal life, as proved by the enormous distention of the bladder with urine at the time of delivery.

### Case Report

Mrs. R. B., aged 23 years, gravida iii, para ii, was admitted to St. Elizabeth Hospital June 17, 1947. Expected date of delivery was July 21, 1947. The first two children had no physical anomalies. The patient had made two prenatal visits to her physician: the last visit was the day before hospital admission and the first visit four weeks previously. Physical examination, pelvic measurements, and routine laboratory findings were essentially negative at the first visit. In the interval of four weeks between the two visits, the patient gained 13½ pounds, blood pressure became elevated to 148/90, there was 2 plus edema of the feet and ankles and a trace of albumin. There was a very marked increase in the size of the abdomen, arousing suspicion of hydramnios.

The first stage of labor progressed normally. In the second stage of labor, the head descended and was delivered spontaneously, but after delivery of the anterior shoulder further descent stopped completely. On pelvic examination, it was ascertained that a greatly distended fetal abdomen prevented any further progress. Under manual guidance, the fetal abdomen was incised, with evisceration contemplated. However, on entering the abdominal cavity, there was escape of straw-colored fluid. After drainage of 3,800 c.c. fluid, the delivery was completed; 400 c.c. fluid remained in the bladder, making a total of 4,200 c.c. measured urine drained from the bladder. Fig. 1 demonstrates the size of the distended abdomen.

An autopsy was obtained on the infant. The positive findings were confined to the greatly distended abdomen with the dilated bladder. The external genitals were essentially negative. The bladder wall was extremely thin and the lining showed crusting and calcified deposits. The ureteral orifices were located with difficulty and the ureters showed a saccular dilatation. The ureters led upward into relatively normal-sized kidneys which showed only moderate hydronephrosis on cut surface. The cut surface of the left renal parenchyma showed definite fibrous and inflammatory changes. Careful examination of the lower urinary tract revealed a patulous internal sphincter leading into a dilated distorted posterior urethra. A probe could be passed through the entire length of the urethra. It was noticed that there was an elongation of the posterior urethra. Gross appearance of the organs is shown in Fig. 2. Explanation of the obstruction has three possibilities: 1. A thin membrane ruptured by the probe but not noted. 2. A redundant fold of mucosa from the elongated urethra forming a mechanical obstruction over the orifice of the urethra. 3. An adynamic type of obstruction might have played a part initially, but unlikely in the absence of any central nervous system disease.

*Microscopic Findings:*—Kidneys: sections of the kidneys show definite evidence of obstructive renal disease. In some areas, the glomeruli are quite normally formed, but throughout there is some increased cellularity and congestion. In focal areas, complete

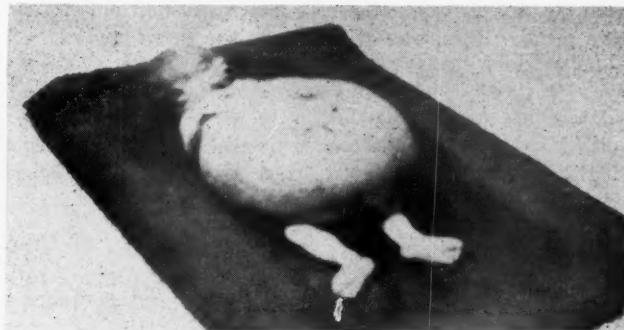


Fig. 1.—Bladder refilled with fluid after delivery, demonstrating the abdominal distention which obstructed vaginal delivery.

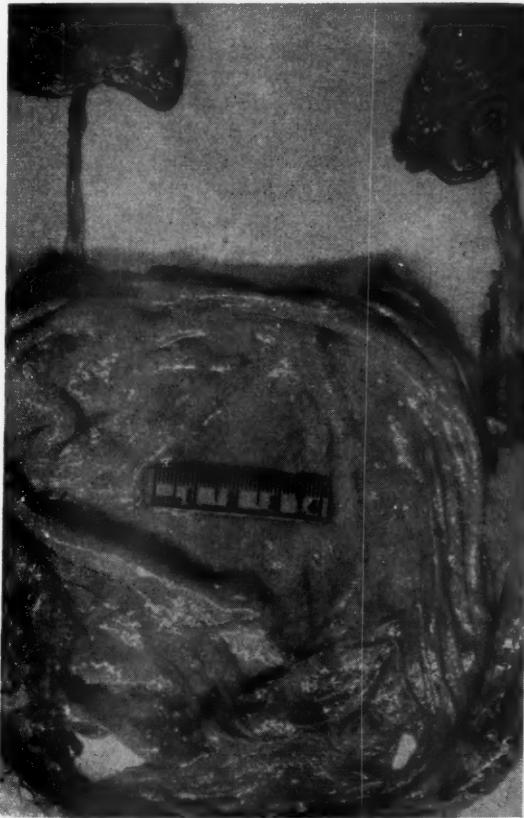


Fig. 2.—Cut surface of bladder, ureters, and kidneys.

atrophy of glomeruli structures with associated tubules is encountered. It would appear that the renal changes are secondary to a long-standing obstruction rather than playing a part in its cause.

*Urinary Bladder and Urethra:*—Sections of the urinary bladder show a marked thinning of the bladder wall with fibrous and hyaline changes in the wall and mucosa. The

hyaline changes have progressed to the point of actual calcific deposits on the surface of the bladder. While there is no bacterial clump, definite chronic inflammatory changes are present. In the region of the prostatic urethra, marked fibrous inflammatory changes are present, with some focal calcific deposits. The changes in the bladder are almost certain to be secondary to obstruction with overdistention, but those in the posterior urethra may be more primary than was apparent on the gross studies.

*Summary of Anatomic Findings:*—

1. Massive dilation of urinary bladder.
2. Compression of abdominal and thoracic viscera by distended urinary bladder.
3. Bilateral hydroureter.
4. Early hydronephrosis with pyelonephritis.

### Fetal Kidney Function

The kidneys are functioning at birth and one frequently observes urination within a very short time after the birth of an infant. Knowing that the infant is often born with a full bladder, we can only speculate on how frequently the fetus urinates during the last months of intrauterine life and in what quantities urine is excreted.

Authorities are in agreement that urinary excretion begins at the fetal age of about three months. Excretion is scant and continues at a retarded rate because the fetus is not dependent on this avenue of elimination. Removal of waste products from the fetus rests upon the placental circulation.

Specific evidence concerning the quantity of urine secreted is best observed in obstructive lesions where the urine is retained. In cystic kidneys, the secretory portion of the uriniferous tubules has failed to unite with the collecting portion of the tubules. Urine is secreted but it is retained in these blind tubules. Such kidneys may enlarge to huge proportions and be the cause of a serious dystocia in the second stage of labor. The case of the infant reported is of a different nature, the child having a normally developed upper urinary tract but an obstruction preventing escape of urine from the bladder. This infant having normal kidneys should be representative of normal fetal physiology. A fetus with a polycystic kidney has a developmental defect of the kidney itself, and this probably does not represent normal function.

In a normal fetus, there are several possibilities in the disposal of the urine that finds its way to the bladder. In early fetal development, the cloaca becomes divided into two parts by the urorectal fold. The ventral portion becomes the urinary bladder and the dorsal portion becomes the rectum. When this septum forms, the cloaca is a blind pouch, but soon the cloacal membrane ruptures, establishing the urogenital and anal orifices. Urine excreted after the establishment of the urogenital orifice may then be voided into the amniotic fluid. In the opinion of most authorities, the fetus drinks amniotic fluid and thus keeps the volume of the fluid within normal limits. It is possible that our case may have had a thin persistent urethral membrane which was ruptured by probing, but was not noted on gross examination.

Another possible means of disposal of urine from the fetal bladder is by reabsorption. The allantois which later is a portion of the urinary bladder develops a rich plexus of vessels in its walls at an early age. This plexus of arteries and veins connects directly with the main circulatory channels of the embryo and may, for at least certain periods, absorb urine from the bladder. The allantoic stalk eventually becomes reduced to the urachus toward the direction of the umbilicus. At times an umbilicourinary fistula may persist at birth.

In summarizing, this infant had a greatly distended bladder containing 4,200 c.c. urine. The kidneys were essentially normal except for secondary changes due to secreting against pressure. The volume of urine found in the bladder of this infant may be a clue to the approximate amount secreted by all fetuses during the last months of intrauterine life.

## **FOUR CASES OF GRANULOMA INGUINALE OF CERVIX DIAGNOSED CLINICALLY AS CARCINOMA\***

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**I**N THE woman, granuloma inguinale produces an ulcerative lesion which most frequently involves the inguinal region and external genitals. Other areas, however, may be involved. When the disease attacks the cervix, it bears a striking resemblance to carcinoma but, fortunately, offers a vastly better prognosis. The gross appearance of the ulceration may vary from a simple, raised, granular lesion to a distinctly polypoid and fungating one. It may be soft or indurated and, though extensive, is always sharply circumscribed. The process may involve the deeper tissues, producing extensive parametrial induration with a resulting frozen pelvis. Bleeding is frequently provoked by trauma and the patient may complain of irregular vaginal bleeding and discharge. Like carcinoma, it spreads by direct extension as well as by lymphatics. In addition, cases of distant osseous involvement have also been reported.<sup>1, 2, 3</sup> While a hematogenous spread had been considered likely, only recently has this been conclusively proved by Packer, Turner, and Dulaney<sup>4</sup> who have succeeded in demonstrating the presence, in blood cultures, of an organism having the morphologic appearance of Donovan bodies.

The diagnosis of granuloma inguinale can be established by finding the Donovan bodies in the pathognomonic cell, a large mononuclear cell with a foamy cytoplasm. Material can be obtained with a curette or biopsy punch, preferably from the expanding border of the ulceration, and stained with the Wright, Giemsa, Dieterle or Mortara stain.

**CASE 1.**—B. S., a 17-year-old Negro single girl, para i, gravida i, was admitted with the chief complaints of lower abdominal pain and vaginal bleeding. On a previous admission, she had been treated for an acute salpingitis, cervicitis, and urethritis. Menstruation had always been completely irregular and for the past year there had been considerable dysmenorrhea. Three days after the onset of the present episode of vaginal bleeding, the patient developed sharp intermittent lower abdominal pain.

On admission, there was tenderness in both lower quadrants with considerable voluntary spasm. Vaginal examination revealed a two-finger introitus with excellent perineal support. The cervix was anterior, conical, and closed. On the anterior lip was a palpable irregularity which felt not unlike another external os. The uterus was normal in size, and retrodisplaced with limited mobility. The adnexa were thickened, prolapsed, and somewhat tender. On rectovaginal examination, there was some tender induration high up in the cul-de-sac. Speculum examination revealed a 1½ to 2 cm. red, granular ulceration on the anterior lip and a smaller one on the posterior lip of the cervix. The borders were raised and bleeding was readily provoked on manipulation, simulating a friable carcinoma. While under observation the entire ulceration became more exuberant.

The admission temperature was 101° F. and pulse 108. Serologic tests for syphilis were negative. Dark-field examination of serum obtained from the ulceration was negative. The Frei test was positive.

\*Presented at a meeting of the New York Obstetrical Society, Feb. 10, 1948.

A biopsy taken from the cervical ulceration was reported as a subacute cervicitis. Donovan bodies were detected in tissue taken from the edge of the ulceration. Under Fuadin therapy, the process healed completely.

CASE 2.—M. K., a 34-year-old Negro widow, para ii, gravida ii, was admitted, complaining of vaginal bleeding and cramps for two weeks prior to admission. Menses were normal until 14 weeks ago, at which time the patient had her last regular menstrual period. Vaginal bleeding started two weeks prior to admission: amounts varied and were at times profuse. Attempted induction of abortion was denied.

Physical examination on admission revealed an acutely ill Negro woman with a temperature of 101.4° F. and pulse 120. The general examination was not remarkable. The lower half of the abdomen was moderately distended with no palpable masses. Pelvic examination revealed an enormously enlarged cervix which was moderately soft and bled profusely on touch. The uterus was not completely outlined, due to extensive parametrial induration. Speculum examination showed the cervix filling the entire vault of the vagina and covered by an exuberant polypoid ulcerative process from which free bleeding occurred. There was no rectal involvement.

The admission diagnosis was carcinoma of the cervix and abortion, probably complete. The biopsy report showed acute and chronic cervicitis with no evidence of malignancy. Serologic tests for syphilis revealed strongly positive reactions. Dark-field examinations were negative. The Frei test was strongly positive. Examination of material obtained by biopsy and stained with Wright's stain revealed the presence of Donovan bodies.

Under Fuadin therapy and several exposures of x-rays delivered by a vaginal cone, there was some improvement, but considerable ulceration still persisted. Streptomycin, 1 Gm. four times daily for five days, brought about a marked improvement. At the time of discharge, there was still a 1 cm. area of ulceration on the posterior lip of the cervix, the entire cervix was much smaller in size, and, while still moderately fixed, was much more mobile than on admission. Considerable parametrial induration remained on the left side. When she was observed later in the Out-Patient Department there was a moderate amount of residual parametritis but the cervix appeared completely healed and menstrual periods were normal.

CASE 3.—E. F., a 35-year-old, married, Negro woman, para iii, gravida iii, was admitted with the chief complaints of leucorrhea of twelve months duration and intermittent vaginal bleeding of five months duration.

Five years prior to admission she had been treated for syphilis. Three years previously a posterior colpotomy had been performed at another institution. About one year before the present admission, the patient had been cystoscoped because of hematuria and a right hydronephrosis was found but no etiological factor for this condition was given in the hospital report. Two months prior to her present admission, the patient was seen at an institution where a tentative diagnosis of carcinoma of the cervix was made pending the report of a biopsy which, however, indicated simply a marked chronic inflammation.

Examination on admission to Bellevue Hospital revealed nothing essentially abnormal except for the gynecologic findings. There was a good parous pelvic floor. The cervix was markedly enlarged and indurated, and on the surface could be felt many firm, irregular nodules. The posterior vaginal wall behind the cervix was adherent to underlying scar tissue, probably the result of the previous colpotomy. The uterus was apparently normal in size with considerable parametrial thickening, particularly on the right side. The adnexa could not be distinguished. Speculum examination showed the entire surface of the portio-vaginalis replaced by an extensive granular ulceration with a nodular surface which bled readily. A tentative diagnosis of carcinoma of the cervix was made, and a biopsy performed, which showed a subacute and chronic cervicitis but no evidence of malignancy. The Frei test was positive and the Wassermann was reported several times as anticomplementary. A biopsy revealed the presence of Donovan bodies. The patient was given Fuadin, 5 c.c. three times weekly. After a three weeks' course of this medication, the ulceration was almost completely healed.

CASE 4.—L. P., a 23-year-old, single, Negro woman, para i, gravida i, was admitted with the chief complaints of irregular vaginal bleeding, discharge, and bilateral lower abdominal pain. For several weeks prior to admission, she was attending a cancer clinic, where a tentative diagnosis of carcinoma of the cervix was made. Repeated biopsies were taken and all were reported as showing evidences of a granulomatous inflammatory process. Since no treatment was offered at this clinic, the patient came to Bellevue Hospital. At the time of admission the general examination was essentially negative. Pelvic examination revealed a two-finger introitus, with a large fungating mass replacing the cervix and filling the entire vault of the vagina. The fundus was small, and seemed to be fixed anteriorly. On the posterior vaginal wall, about 1½ inches from the introitus, was a raised ulceration which extended upwards to involve the entire posterior and lateral walls of the vagina. The process had a raised, irregular edge, was comparatively soft but friable, and bled readily. There was extensive rectovaginal septum induration as well as bilateral stony-hard parametrial involvement.

The Wassermann test was 4 plus and the Frei test was negative. Examination of tissue stained with the Wright and Mortara stains revealed Donovan bodies. The patient was given Fuadin, 5 c.c. intramuscularly three times weekly, and some x-ray therapy. After a month of this regime considerable improvement was noted. The posterior and lateral vaginal walls were completely healed. The cervix could be readily identified and showed patchy areas of epithelialization although the parametrial induration persisted. Subsequently, the cervix healed completely but considerable residual induration of the parametrium was still noted after several months.

### Summary

Four cases of granuloma inguinale of the cervix have been reported. They illustrate the marked similarity between this process and carcinoma, in that patients complain of vaginal discharge, irregular bleeding, and perhaps lower abdominal pain, while examination reveals ulceration of the cervix which bleeds readily on manipulation. Frequently there is extensive parametrial induration as well. However, examination of suitably stained material, preferably from the edge of the ulceration, discloses the identity of this process. Granuloma inguinale is characterized by the presence of a chronic inflammatory process with a pathognomonic cell containing Donovan bodies.

In all cases where carcinoma of the cervix is suspected clinically, but is not confirmed by histologic study, properly stained material should be examined for the presence of the "granuloma" cell and its Donovan bodies.

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## UNRUPTURED OVARIAN PREGNANCY

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OVARIAN pregnancy is much more common than many assume. The total number of cases reported in the literature up to January, 1947, was eighty-eight.

In some of the cases that have been reported, a long period of sterility preceding ovarian pregnancy has been noted, as well as the presence of a co-existing endometriosis.

The patient is a married woman, aged 30 years, well nourished, normally developed, and of medium build. She had an appendectomy at the age of 13 years, after several attacks of what was diagnosed as recurrent appendicitis. She had the usual childhood diseases, without complications. Patient had been married for nine years, was never pregnant, and had never used contraceptives.

Menstrual history: onset at 11 years of age, duration 3 to 4 days. Her menstrual periods have been irregular in recurrence since onset, usually had an interval of 42 to 46 days between periods. At times, she experienced cramplike lower abdominal pain with headache before the flow was established, but never experienced severe pain, and has always been able to perform her usual duties without much discomfort throughout the period, and her blood loss was moderate in amount.

Her last normal menstrual period was from Sept. 3 to 7, 1947. She noticed a vaginal discharge on October 16, 1947, and passed a few small clots. She described the discharge as dark in color, and scant in amount for the first day of a period, but was of the opinion that this was the start of a normal period beginning as usual about 14 days late. She continued to have menstrual bleeding after the usual three days. About the fifth day, she developed pain, cramplike in character, in her lower abdomen. She stated that she had "contracted a cold" and attributed her lower abdominal pain to "sore abdominal muscles."

The patient came to my office Nov. 14, 1947. She stated that she had continued "menstruating since October 16, 1947, and was advised by friends to consult a physician about it."

Her temperature was 98.2° F., pulse 84. Blood examination red blood cells 3,600,000, hemoglobin 76 per cent, white blood cells 7,700 polymorphonuclear leucocytes segmented 69 per cent; polymorphonuclear leucocytes nonsegmented 10 per cent; lymphocytes 17 per cent; monocytes 2 per cent; eosinophiles 2 per cent. Blood serology was negative by both Wassermann and Kahn tests; Rh factor was positive. Blood type B or 3. Catheter specimen of urine revealed the presence of 1 to 2 white blood cells per high-power field and a few squamous epithelial cells. Albumin and sugar negative.

Examination of the abdomen disclosed moderate tenderness over the lower right abdomen. Vaginal examination revealed a scanty bloody discharge. Introitus was marital, nulliparous in type. Speculum examination of the cervix showed a mild erosion involving the endocervix and a Nabothian cyst on the anterior lip. The cervix was not particularly soft in consistency. The fundus was anterior. The uterus was slightly enlarged for a nullipara, but not unusually soft in consistency, and was freely movable, but displaced to the left by a soft cystic mass about 7 cm. in diameter, in the right adnexal region. The mass was tender to palpation and fixed in the cul-de-sac. A diagnosis of right ovarian cyst was made and operation was advised. While waiting for a hospital bed, the patient returned to her home about 20 miles from the city. On Nov. 18, 1947, she complained of severe abdominal pain, intermittent and cramplike in character, and passed material from the vagina and was having

rather free vaginal bleeding. A local physician was called to her home and notified me that he thought that she was having an abortion, since the material passed had the gross appearance of decidua.

Pathologist's report: decidua.

The patient was admitted to the hospital Nov. 20, 1947, and was re-examined. The tender right adnexal mass was no larger. The uterus was of the same size and consistency as at the previous examination, but because of the passage of decidual tissue, a diagnosis of ectopic pregnancy was made and operation advised. With the patient under sodium Pentothal and spinal anesthesia, a low midline incision was made and the abdomen opened. The omentum was found attached to the right adnexal mass but was readily freed. The mass occupied the position of the right ovary, was about 8 cm. in diameter, and was adherent to the posterior surface of the broad ligament at the base in the cul-de-sac. The right tube was found stretched over the tumor mass. The left ovary was normal. The left tube showed evidence of an old perisalpingitis, and the fimbriated end appeared to be closed. The uterus was normal in size and normal in consistency but pushed to the left by the right adnexal mass. The mass was freed by finger dissection and removed by clamping, cutting, and ligating the infundibulopelvic ligament, mesosalpinx, and Fallopian tube.

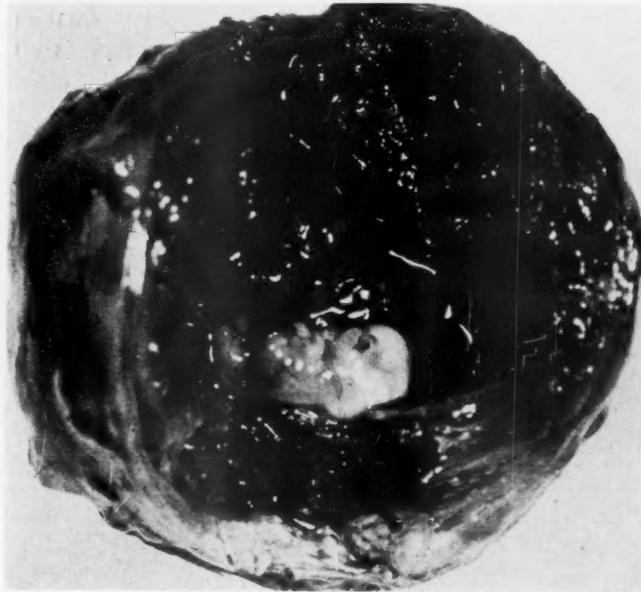


Fig. 1.—Ovarian mass opened, showing an embryo 2.5 cm. in length.

The tumor, after removal, had the gross appearance of an endometrioma of the ovary. Careful inspection of the cul-de-sac, uterosacral ligaments, and the peritoneum covering the rectum and sigmoid did not disclose any evidence of ectopic endometrial implants. The left ovary was normal. The specimen was incised and a spherical cavity was found in the center of the tumor. The sac lining the cavity was incised and found to contain an embryo. The sac was filled with clear liquid, lined by a smooth, glistening membrane. The embryo was curled and supported by filmy membranes and a clearly distinguishable body stalk attached near the caudal end. A postoperative diagnosis of unruptured ovarian pregnancy was made.

*Pathologist's Report—Gross.*—Specimen of ovary measuring 8 by 8 by 6 cm. A Fallopian tube is attached to the ovarian mass. The tube is dissected throughout its course and found to open freely to its fimbriated end, which is adherent to the surface of the ovarian

mass. There is no abnormality of the mucosa which would suggest a decidual reaction. Section of the ovarian mass reveals a cavity 6 cm. in diameter, which contains an embryo 2.5 cm. in length. The wall of the cavity is hemorrhagic and measures 2.5 to 1 cm. in thickness. The mucosa shows no abnormality.



Fig. 2.—Photomicrograph of tissue surrounding the sac, showing follicle cyst at right ( $\times 12$ ).

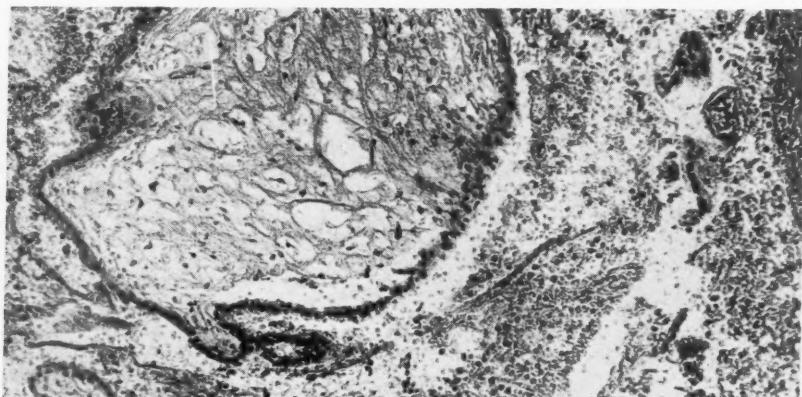


Fig. 3.—Magnification of area outlined in Fig. 2, showing chorionic villus ( $\times 130$ ).

*Microscopic.*—Section from ovarian mass reveals ovarian tissue with decidua and chorionic villi and hemorrhage. In the section of the tube adherent to the ovary, there is a small focal area of decidua but no chorionic villi. This decidua is similar to the decidua found in the specimen passed per vaginam. Inasmuch as decidual change occurs in other organs in ectopic pregnancy, it may be concluded that this represents such a change. Although the finding does not completely exclude the possibility that this ovarian pregnancy had its origin at an earlier period in the Fallopian tube, this latter conclusion is rather remote.

*Diagnosis.*—Compatible with primary ectopic ovarian pregnancy.

#### Comment

The passage of a decidual cast per vaginam, which microscopically showed the presence of decidua with an absence of chorionic villi might have established the diagnosis of ectopic pregnancy. However, the old theory that, in the presence of ectopic pregnancy, the endometrium always undergoes decidual transformation cannot be maintained. The absence of decidual tissue in the uterus cannot be used as a diagnostic criterion, while, conversely the presence of decidual tissue without intrauterine pregnancy is practically always indicative of ectopic gestation, since its only alternative cause is the very rare corpus luteum cyst.<sup>1</sup> The

consistency of the cervix and uterus on examination and lack of early symptoms of pregnancy were misleading. The formation of decidua in the normal tube during pregnancy is unusual, but according to Kermauner, decidua is found in about 15 per cent of tubes. That a limited decidual reaction may occur, however, has been shown by Williams,<sup>2</sup> who found decidual cells in the opposite tube, where they could not be confused with cells of fetal origin.

The macroscopic and microscopic examination of the specimen proves it to be an unruptured ovarian pregnancy, and is compatible with primary ectopic ovarian pregnancy. The small focal area of decidua found in the section of the tube adherent to the ovary did not contain chorionic villi, and resembled the decidua found in the specimen passed through the vagina which did not show chorionic villi. There is a possibility that this ovarian pregnancy may have had its origin at this site in the Fallopian tube, but this seems rather remote.

The pathologist was unable to find any evidence of endometriosis in the sections studied. It is interesting that this patient gave a history of a long period of sterility prior to the ovarian pregnancy and that the microscopic examination of the specimen showed follicle cysts, varying in size, in the portion of the mass with intact stroma—a finding which has been noted in other reported cases.

Dr. John W. Howard, Pathologist, Delaware Hospital, Wilmington, Del. made the pathologic examinations.

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2222 WEST SEVENTEENTH STREET

## BILATERAL OVARIAN FIBROMA

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ACCORDING to recent reports fibromas constitute from 1.5 to 5 per cent of ovarian neoplasms.<sup>1-3</sup> In the series studied by Dockerty and Masson, about 10 per cent of ovarian fibromas were bilateral.<sup>1</sup> The relation of ovarian tumors and of fibromas in particular to the presence of fluid in the peritoneal and pleural cavities, the so-called Meig's syndrome, is the subject of numerous communications.<sup>4, 5</sup> In this paper the clinical history is presented of a woman past 70 years of age who had large bilateral ovarian fibromas; their presence was not associated with ascites and hydrothorax.

C. M. E., a white woman, aged 73 years, was admitted to the University of Oklahoma Hospitals, Sept. 25, 1945, with complaints of pain and masses in the abdomen and loss of weight and strength. She stated that about three years prior to admission she first noticed a mass about the size of a golf ball in the right lower abdomen. About two months later another similar mass appeared on the left side. These masses enlarged progressively and apparently increased in size more rapidly during the past one and one-half years. During the past few weeks pain appeared radiating into the right lower limb, and became severe, limiting her activities. She had lost some weight and strength.

Menarche occurred at the age of 16 years, the interval was regular, lasting twenty-six days, with the flow four to five days. She had seven pregnancies with no abortions, and reached the menopause at the age of 45 years. She had always been in good health and had no previous operations.

At the time of admission she was well developed, well nourished, and appeared about ten years younger than her stated age. She was not acutely ill. The temperature was 99.4° F.; the pulse rate was 88; the respiratory rate 20; the blood pressure was 150/100. The abdomen was medium sized and flat. In the lower abdomen three masses were visible and palpable, one on the left was about 12 by 9 cm., another just above the symphysis pubis was smaller and not freely movable, the third, which was 17 by 12 cm., was on the right and extended up toward the flank. This mass was freely movable and the site of its attachment could not be determined. There was moderate tenderness on palpation. Pelvic examination revealed a parous introitus with the cervix scarred bilaterally. There was no discharge. Movement of the left and suprapubic masses was transmitted to the cervix. There seemed to be no connection between the right mass and the pelvic organs.

The urine was yellow, turbid, acid, with a specific gravity of 1.017, and with no albumin and no glucose. There were 20 white blood cells per h.p.f. The red blood cell count was 4,140,000, the hemoglobin content 13 Gm., the white blood cell count was 8,400 with granulocytes 74, and lymphocytes 26 per cent. The Mazzini test of the blood was negative. Retrograde pyelograms on October 2 revealed both kidneys to be of normal size, shape, and position, with no changes in the calices and renal pelvis. Smears of the urinary sediment of the right kidney contained no organisms; a few gram-negative bacilli were seen and cultured from the urine of the left kidney. Electrocardiogram examination on October 4 disclosed primary T-wave changes of a nonspecific kind, not considered a contraindication for operative procedure. Roentgenologic examination revealed no fluid in either pleural or pericardial cavity; calcification of the aortic and mitral valves and of the

abdominal blood vessels was seen. Examination of the gastrointestinal tract disclosed complete emptying of the stomach in five hours, diverticula of the colon and no connection of the pelvic masses with the digestive tract.

Laparotomy on October 5 (by Dr. Oscar R. White) disclosed replacement of each of the ovaries by similar, firm, globular masses. That on the right was about 5, that on the left 4 inches in diameter. The uterus was of usual size and appearance. The Fallopian tubes were stretched over the respective ovarian masses. There was no excess fluid in the peritoneal cavity. A bilateral salpingo-oophorectomy and appendectomy were performed. The postoperative course was uneventful and the patient was discharged October 23, the eighteenth day following the operation. When last seen March 23, 1946, five months after the operation, she was well and had no pertinent complaints.

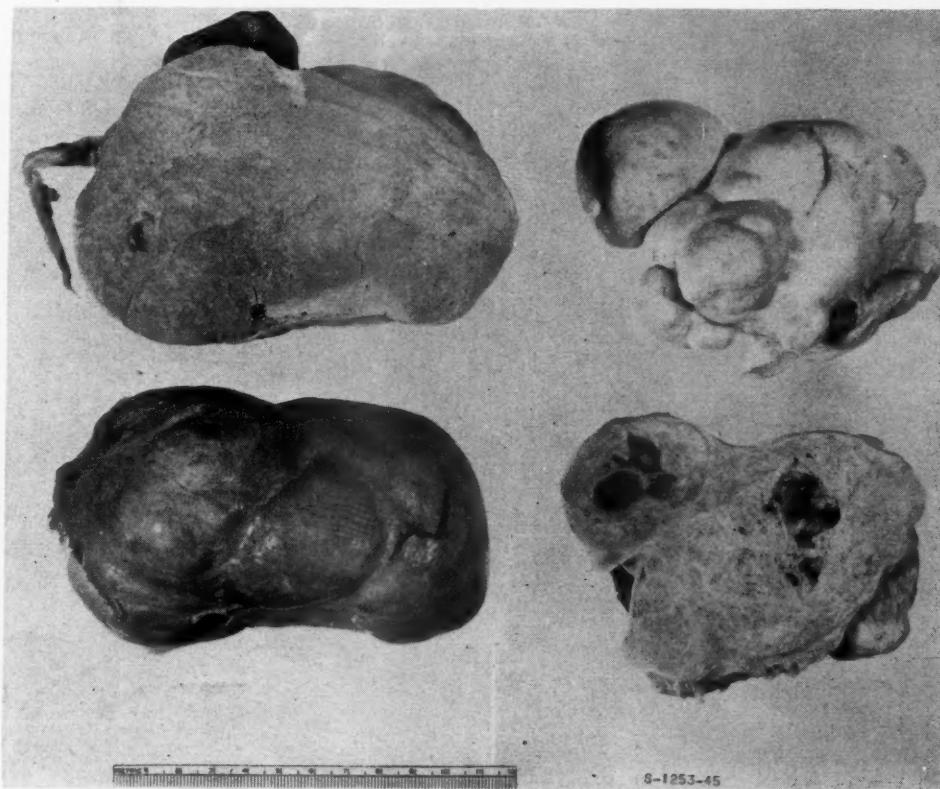


Fig. 1.—Gross appearance of the ovaries externally and on their cut surfaces. The larger one is the right ovary.

The specimen consisted of both Fallopian tubes and ovarian masses and the appendix. In place of the right ovary there was a solid lobulated mass measuring 12.5 by 10 by 8 cm. and weighing 610 grams (Fig. 1). The surface was smooth and shiny. The cut surfaces were uniform gray white with a delicate fibrillar pattern. No areas of softening or discoloration were evident. The Fallopian tube measured 12 by 1 by 0.4 cm.; its fimbriated end was patent, it appeared somewhat stretched and laterally compressed. The mesosalpinx was delicate. The left ovary was replaced by a solid mass, 10.5 by 9.5 by 7 cm. weighing 324 grams. It resembled the right except that the surface of the ovarian mass was more lobulated; the lobules measured 3 to 5 cm. in diameter. The cut surfaces had a similar or more coarse fibrillar pattern with occasional cavities from 0.5 to 2 cm. in diameter.

containing a thick, clear, or hemorrhagic liquid (Fig. 1). The left Fallopian tube with mesosalpinx resembled the right. The appendix was 3 by 0.5 cm. and part of its lumen was obliterated.

Microscopic preparations from various parts of each of the ovarian masses disclosed round or elongated cell nuclei within a delicate fibrillar ground substance in an interlacing arrangement closely resembling ovarian stroma (Fig. 2). Elsewhere the texture was loose; the fibrils were spread apart with occasional collagenous bundles and with cells having vesicular nuclei and a stellate cytoplasm fading into the fibrillar ground substance (Fig. 3). Hyaline change was more marked in some fields than in others. There were also extensive areas of lavender stained granular deposits in the larger hyalinized fields. Apparent remains of corpora albicantia appeared here and there. Over extensive areas a cellular débris was encountered fading into the adjacent tissue with hardly any cellular reaction.

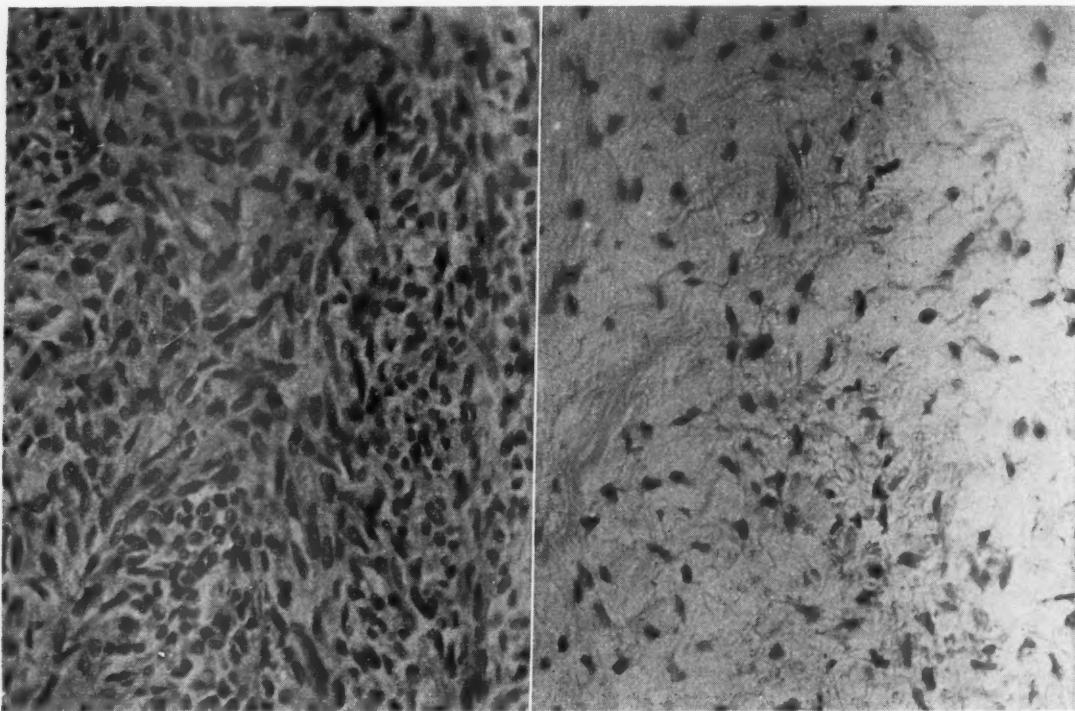


Fig. 2.

Fig. 3.

Fig. 2.—Microscopic appearance of the ovarian neoplasm. Round or elongated cell nuclei are seen in a steam or whorl-like arrangement within delicate fibrils. ( $\times 300$ .)

Fig. 3.—Microscopic appearance of the ovarian neoplasm. Cells with vesicular nuclei and a stellate cytoplasm are seen fading into a fibrillar ground substance. ( $\times 300$ .)

### Comment

Ovarian neoplasms occur in all decades of life, but are more frequent during the reproductive period.<sup>3</sup> The stimulation for the cyclic changes in the ovaries is known to be extrinsic. The parent cells of most neoplasms occurring in the ovaries arise from the germinal epithelium or its derivatives. Therefore it is safe to assume that hormonal stimulation is responsible for the reaction of the germinal epithelium. Ovarian neoplasms are comparatively rare in children before the onset of menstruation and in women after the cessation of menstruation. The hormonal influence regulating ovarian function is least potent during postmenopausal life. Neoplasms arising in the ovary at this period of life are therefore usually of stromal origin.

Our patient was past the seventh decade of life. The large growths in the ovaries were almost alike with identical microscopic structures and with complete absence of epithelial elements.

### Summary

Fibroma of both ovaries is reported in a 73-year-old white woman. The large growths appeared grossly almost alike and microscopically they mimicked ovarian stroma. They contained no epithelial elements. There was no associated ascites and hydrothorax.

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## ENDOMETRIOSIS OF THE VAGINA FOLLOWING VAGINAL HYSTERECTOMY

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THIS is a case report of endometriosis of the vagina following vaginal hysterectomy. Because of its rarity, we felt it worth while reporting.

In a review of 800 cases of vaginal hysterectomies at the Cook County Hospital, we failed to find a similar complication; also Green-Armytage 627 cases; N. Sproat Heaney 627 cases; 517 cases by Danforth; 305 cases by Tyrone and Weed; 210 cases by Cofer; and 500 cases by Falk and Bunkin failed to reveal a similar complication. However, we did find one case report in the *Polish Medical Gazette*.<sup>1</sup>

### Case Report

A 39-year-old Negro woman, of good general health, was admitted to the Gynecological service of Cook County Hospital in March, 1945, with a complaint of excessive vaginal bleeding for seven days past. History revealed a change in the menstrual habits of the patient in the preceding three months, her flow becoming excessive in amounts and persisting for a longer period, up to eight days. Past menstrual history indicated that at the age of 14 years the menarche began, it being characterized by a regular cycle of five days, moderate flow, with no dysmenorrhea either primary or acquired. Obstetric history revealed a gravida iv, para iii, including a normal spontaneous delivery in 1923, a breech delivery in 1924, and a normal spontaneous delivery in 1926. There was a three months spontaneous abortion in 1925. Pelvic examination elicited a small, nodular corpus, freely moveable, not tender, adnexal findings not revealing, and a relaxed posterior vaginal wall. Other physical findings were noncontributory, or otherwise negative. Blood pressure was 120/80, pulse was 84, respirations were 20, and temperature was 98.6° F. Hemoglobin was 75 per cent, 4,300,000 erythrocytes, 8,100 leucocytes, urine negative, and negative serology.

A vaginal hysterectomy without morcellation and a posterior colporrhaphy were performed. The postoperative course was uneventful. The patient left the hospital in good condition, symptom free. Final postoperative six-week examination was essentially negative.

Three months following the vaginal operation the patient noted what seemed to her to be a return but definite diminution of her menstrual periods. There was a show of blood which was cyclic in its appearance, in keeping with her previous menses. After two years and seven months of these cyclic episodes following her vaginal hysterectomy, the patient presented herself for examination to the outpatient Gynecological Clinic of Cook County Hospital in October, 1947.

Pelvic examination revealed a free pelvis: no masses, no fixations, no tenderness. Speculum examination revealed a flat, bluish area, about 4 by 6 mm., on the left posterior vaginal wall, immediately below the transverse hysterectomy scar (Fig. 1). The remainder of the vaginal vault was without findings. Suspicions were immediately aroused of the possibility of an endometriosis of the vagina. A biopsy of this suspected area was taken for histologic study. The biopsy report showed an endometriosis of the vagina (Fig. 2).

Forthwith, the pathologic report of the corpus and cervix removed at surgery in 1945 was reviewed. No evidence of endometriosis or adenomyosis was present at that time. Cystoscopic and proctoscopic examinations done in October, 1947, have not given indication of other ectopic endometrial implants.

It is quite probable that the endometrium was implanted during surgery.

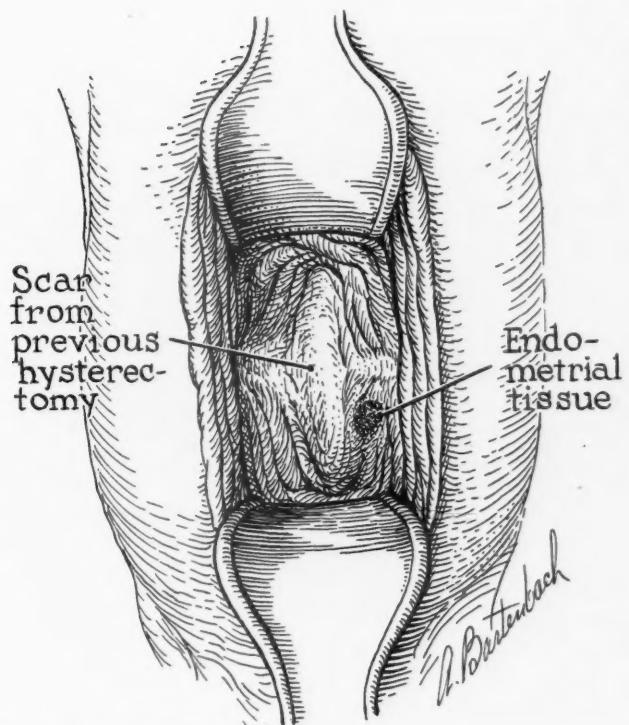


Fig. 1.—Artist's drawing showing the site of endometriosis.

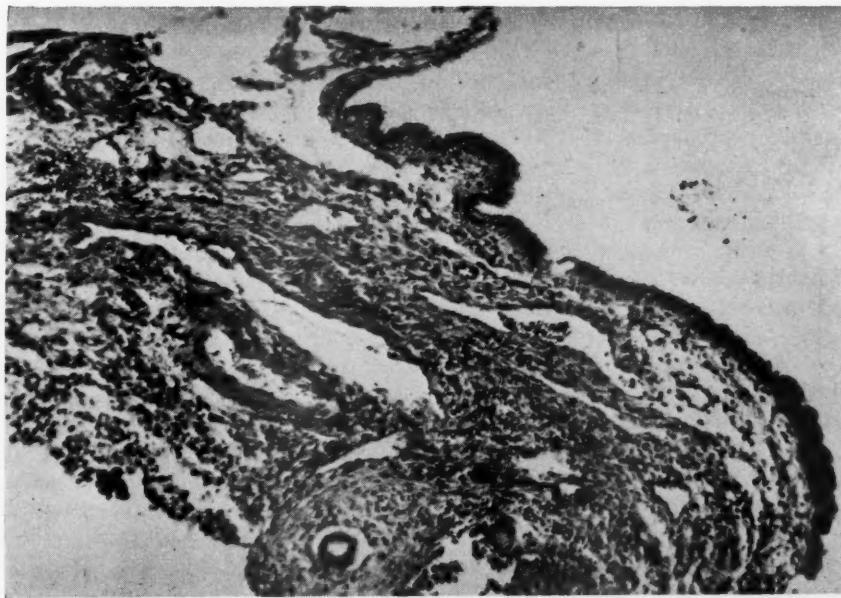


Fig. 2.—Photomicrograph of biopsy showing endometrial tissue (X90).

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## UNSUSPECTED ABDOMINAL CHORIONEPITHELIOMA

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EVER since we lost practically all cases of chorionepithelioma, which were diagnosed only at autopsy, we had been vigilant of their occurrence and, in recent years, have felt the satisfaction of having saved many lives because of early diagnosis, making possible early radical treatment. So our failure to make the correct diagnosis in the present case, though markedly advanced when first seen, showed that we have much yet to learn about chorionepithelioma.

L. P., 27 years old, laundress, entered the Philippine General Hospital on Sept. 13, 1947, because of an abdominal painless tumor. The patient claimed that she first noticed the tumor as an apple-sized mass in the lower abdomen, five months previous to admission. And at the same time, she also noticed that she began to have slight vaginal bleeding which was continuous for two and one-half months but which stopped for two months thereafter. However, the last two weeks before admission, the slight bleeding reappeared off and on. During this time, she also experienced slight afternoon rise of temperature.

She had had three pregnancies, the first two of which ended in full-term deliveries ten years and five years, respectively, before admission. The third pregnancy ended in a four months' abortion one year previous to admission. Menstrual periods after the abortion were normal, the last one occurring one month before the onset of the slight continuous bleeding.

Physical examination showed that she was fairly well nourished though rather thin. Lungs and heart were apparently normal. The abdomen showed a large, firm, painless, slightly movable, globular tumor reaching up to the level of the umbilicus, the size of a six months' pregnancy. On vaginal examination, one could feel a small cervix connected with the uterus which was flattened and pushed to the left and posterior fornices by the large firm mass. There was slight pinkish discharge from the external os.

Red blood count, 3,900,000; white blood count, 9,650; polymorphonuclear leucocytes, 77 per cent; lymphocytes 23 per cent. Urinalysis normal. Blood pressure 110/70.

Because of the finding of a firm, solid painless mass in the abdomen which was independent but intimately connected with the uterus, our first impression was a large subperitoneal fibroid. We could not, however, reconcile the diagnosis of a subperitoneal fibroid and the rapid growth of the tumor, which was noticed only five months previous to admission. But we felt that perhaps the tumor had existed unnoticed for sometime. Because of the rapidity of the growth, we considered the possibility of a malignant tumor of the ovary. Chorionepithelioma was considered, but was immediately dismissed because of the firm consistency of the tumor and because the uterus could be distinctly outlined as separate from it. The patient was, therefore, scheduled for operation three days later. On that day, however, she had cough and fever. In the belief that she was suffering from influenza, she was treated for this condition and the operation was postponed. But the fever, which was irregular, did not abate. On the contrary, as the days advanced, it became higher. Moreover, the patient began to complain of abdominal pain, tympanism, nausea and vomiting. At this time, we thought that what we regarded as a tumor was perhaps an encapsulated abscess which now began to leak into the peritoneal cavity and which needed immediate laparotomy, which was done on Oct. 2, 1947, under local anesthesia.

On making a small incision on the peritoneum, an encapsulated mass looking like a large endometrial cyst was found. Aspiration revealed bloody content. After enlarging the abdominal incision and trying to evacuate the contents, we encountered a bloody mass of many small, firm, loose pieces of tissue attached to the intestines, omentum, uterus and posterior parietal peritoneum. We then thought we were dealing with a malignant growth of the

ovary. But further exploration showed that both ovaries were intact, only that they were cystic. Since most of the bleeding came from the fundus of the uterus, we quickly did a subtotal hysterectomy and double salpingo-oophorectomy. After evacuating as much of the growth as possible and putting a firm gauze packing against the oozing surfaces, the abdominal incision was closed in the usual manner. Unfortunately, we could not give blood transfusion for lack of a donor or blood bank. We gave four units of plasma, before, during, and after the operation, and continuous venoclysis of glucose solution. The patient became conscious after the operation, but succumbed two hours afterwards.

Examination of the hysterectomized uterus showed a raw eaten-up fundus from which issued friable strands looking as if they had been pulled upwards. Sagittal section of the uterus showed that the endometrium was clean without any trace of the growth. Both ovaries had been converted into corpus luteum cysts the size of a goose egg.

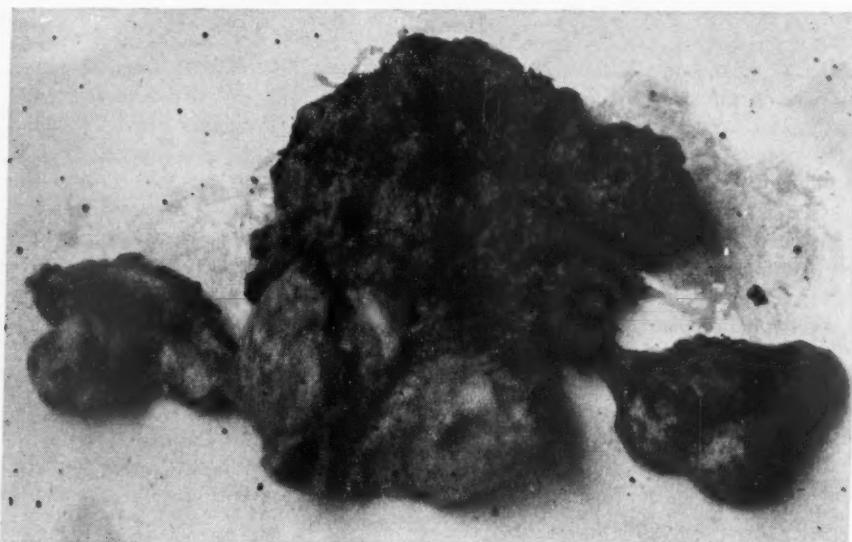


Fig. 1.—Chorionepithelioma. Uterus.

Autopsy revealed two more handfuls of growth attached to the intestines, omentum, and posterior parietal peritoneum. The lower lobe of the right lung showed a small focus of metastasis of the growth. Biopsy of the growth found in the lungs and abdominal cavity showed syncytium and Langhans cells with a predominance of the latter in some portions and of the former in other parts.

*Comment.*—Apparently, the condition began as a myometrial chorionepithelioma which later extended to the right broad ligament and which rapidly grew in size. It was only in the last days, when the chorionic cells had extended themselves beyond the confines of the broad ligament and serous surface of the uterus that internal bleeding, tympanism, abdominal pain supervened rapidly, threatening the life of the patient.

Our inability to make preoperatively the correct diagnosis was due to the following: (1) Because when first seen, the size, consistency, and contour of the growth was suggestive more of uterine fibroid than of anything else. (2) The failure to associate the growth with the four months' abortion which took place seven months before she complained of bleeding. (3) The misinterpretation of the uterine bleeding that occurred later as part of the phenomenon of uterine fibroma. (4) The fact that she was in relatively good condition on admission, in spite of the advanced condition of the growth. Because we erroneously thought chorionepithelioma was a remote possibility, no Friedman test was made. The reason the patient here reported did not have early peritoneal bleeding, in spite of its being a myometrial growth that had gone beyond the uterus, is because the chorionic cells grew within the leaves

of the broad ligament which at first constituted itself as a firm capsule, giving shape and firm consistency to the growth in the same manner as happens in intraligamentous ovarian conditions or even pregnancy.

The long interval of seven months that elapsed between her abortion and the occurrence of the abnormal vaginal bleeding is not unusual. From our experience with myometrial chorionepithelioma, in 55 per cent of the eight cases we had in 1942 to 1945, the vaginal bleeding did not manifest itself until from one year and two months to three years after the passage of the last product of conception which happened to be hydatidiform mole. Two of these cases were preoperatively diagnosed as cancer of the uterine corpus and two, because of symptoms of internal bleeding on admission, as ruptured tubal pregnancy.

Had we seen the patient when she began to have continuous bleeding, had we felt the small mass in the lower abdomen, and associated such findings with her last abortion, we would have been able to diagnose her condition by the clinical method of diagnosis of uterine chorionepithelioma as first described by me.<sup>2</sup> Even if our diagnosis then had been fibroma, she would have been saved by immediate laparotomy, which would have revealed the true condition of the uterus.

If the correct diagnosis of abdominal chorionepithelioma had been made on her admission, what treatment should have been instituted? I believe the only hope for the patient then was x-ray treatment both for the abdominal and pulmonary growths.

The author is greatly indebted to Dr. Apelo, who furnished the photograph of the uterus.

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## BILATERAL SIMULTANEOUS EXTRAUTERINE PREGNANCY\*

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EXTRAUTERINE pregnancies are estimated by Schumann<sup>1</sup> to occur once in every 300 pregnancies. Bilateral simultaneous extrauterine pregnancies occur many times less often. They are considered the rarest form of double-ovum twin pregnancies. Therefore, the occurrence of an authentic case which meets the criteria for acceptance, as stated by Fishback,<sup>2</sup> is rare enough to merit its being reported.

In 1935, Fitzgerald and Brewer<sup>3</sup> reported on 402 cases of extrauterine pregnancies from 1924 through 1934; in 1942, Lash and Kaufman<sup>4</sup> reported on 903 cases through 1940, and Fitzgerald<sup>5</sup> has collected an additional 274 cases from 1940 through 1946, all from this hospital, and in these groups no bilateral double ovum ectopic pregnancy was found. Lash and Kaufman reported on the only instance of an unilateral twin ectopic pregnancy to have occurred at this institution. One of us (R.A.A.) has reviewed the cases of extrauterine pregnancies for the years not included in the above reports for an additional 403 cases. The case herewith, therefore, is the first bilateral simultaneous extrauterine pregnancy to be proved at this hospital in a total of 1,580 extrauterine pregnancies over a twenty-two year period.

Mrs. L. Mc, a 32-year-old, well-developed, well-nourished Negro woman who was not acutely ill, was admitted to the gynecologic service on Oct. 24, 1947, complaining of irregular vaginal spotting for the past two months and a dull lower abdominal pain for the same period. Her last normal menstrual period had occurred in August, 1947. Her September period started at its expected date, continued for two days, stopped for two days, following which the spotting started again and continued for another seven days. Shortly after the onset of this irregular period, the patient noted a dull lower abdominal pain which radiated into both right and left lumbar regions. The next period (October) began several days before its expected date and continued irregularly throughout the month. The abdominal pain remained unchanged.

The patient was a gravida iv, para iii, a spontaneous abortion having occurred in 1940. The menarche began at 13 years, of regular interval, lasting for four days, with no dysmenorrhea.

On admission, the temperature was 98.6° F., pulse 80, respirations 20, blood pressure 110/80. The erythrocyte count was 4,100,000, the leucocyte count 9,550, and the serologic reaction was negative. Abdominal examination revealed moderate tenderness in the right lower quadrant, no masses being outlined. Bimanual examination revealed a tender, cystic, right adnexal mass. The left adnexa felt thickened and was also tender. The corpus was enlarged two to three times its normal size and was firm and nodular. A diagnosis of fibroid uterus with pelvic inflammatory disease was made.

At laparotomy, the corpus was found to be in good position, about twice normal size and nodular. The right tube was drawn backward toward the right infundibulopelvic ligament and had a hemorrhagic mass, measuring 4 by 3 by 3 cm., in its isthmic portion. Its fimbriated end was free and not involved. The left tube was directed downward and backward toward the cul-de-sac, its fimbriated end having been replaced by another hemorrhagic, cystic mass, measuring 6.5 by 3 by 3 cm., which was rather firmly attached to the rectum.

\*Presented before the Chicago Gynecological Society, Jan. 16, 1948.

There was no free blood in the peritoneal cavity. With the pathology at hand and the patient's condition being good, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed.

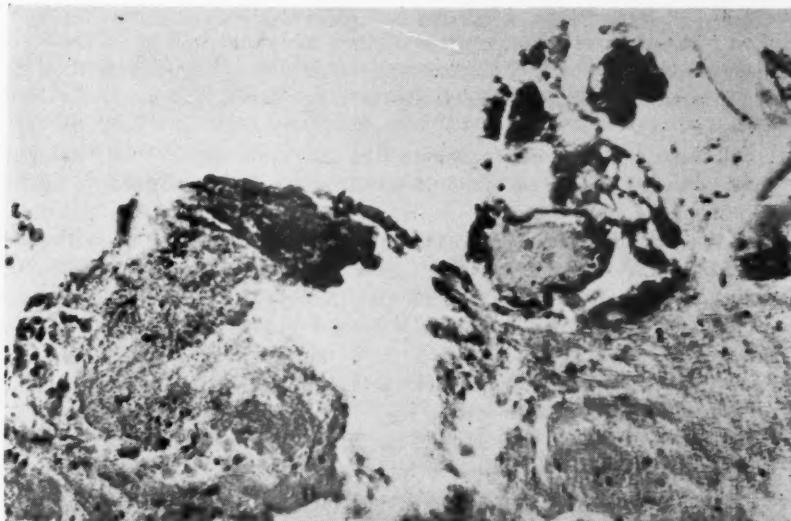


Fig. 1.—Right tube section.

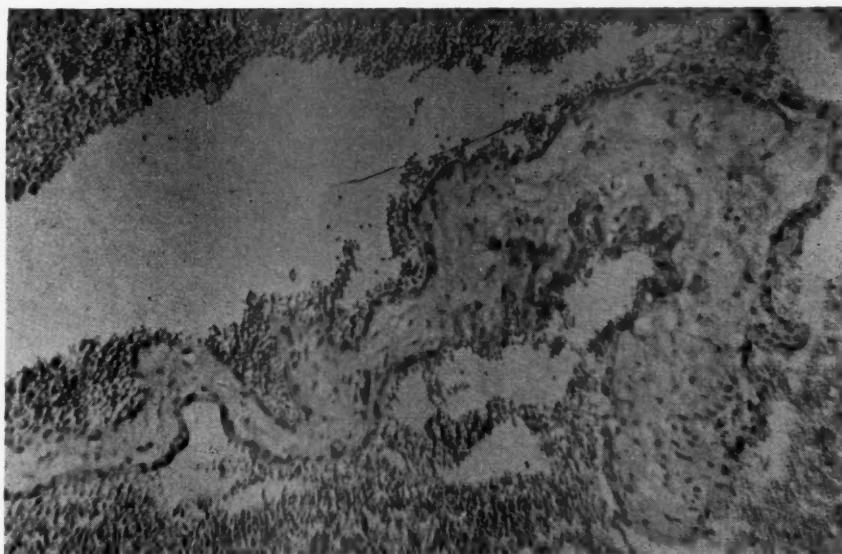


Fig. 2.—Left tube section.

The postoperative course was uneventful and the patient left the hospital in good condition. Microscopic study of the cystic masses in each of the fallopian tubes revealed the presence of chorionic villi, approximately at the same developmental stage, indicating a simultaneous bilateral tubal pregnancy to have been present. (Figs. 1 and 2.)

### Discussion

The review of authentic cases presented by Fishback in 1939 brought the literature up to date and set the standards of acceptance for these cases. Fishback collected 76 cases and reported on one of his own, a twin ectopic pregnancy on the left and a single one in the right tube at the same time. His principles for acceptance require that "there should be a description of the fetuses or any portion of them found, as well as of placental material. A microscopic examination may be necessary to confirm the diagnosis and to give criteria for fixing the pregnancy periods. Especially is this needed where only a hematosalpinx is present grossly."

Harris and Leviton,<sup>6</sup> in 1946, surveyed the literature since 1939 and presented an additional eight authentic cases of bilateral simultaneous tubal pregnancy, making a total of 85, including one of their own.

As far as was possible, the accessible literature was reviewed by us and other authentic cases not included in the above reports were found. They include single cases by Olovson<sup>7</sup> (1938), Pasman and Lovazzano<sup>8</sup> (1938), Froewis<sup>9</sup> (1939), P. Meyer<sup>10</sup> (1939), Tractenberg<sup>11</sup> (1944), Weyeneth<sup>12</sup> (1945), MacDonald and Masters<sup>13</sup> (1946) and Gorman<sup>14</sup> (1947). These cases, plus the one here reported, make a total of 94 authentic cases of bilateral simultaneous tubal pregnancy. Other cases no doubt are included in other foreign literature, but their distribution has been delayed by the recent war.

The preoperative diagnosis of bilateral simultaneous tubal pregnancy is a difficult one to make. Froewis is the only one noted to have made the speculative diagnosis of a "probable bilateral tubal pregnancy." Since the bilaterality of an ectopic pregnancy is so rarely diagnosed before surgery, the practical significance to be stressed is that both adnexa should be inspected and palpated at the time of operation.

We are indebted to Dr. Alex B. Ragins of the Department of Pathology, Cook County Hospital, for his assistance with the microscopic report.

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## INTERSTITIAL PREGNANCY

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**A**MONG the varied types of ectopic pregnancy encountered, one of the least common, but yet more serious varieties, is the interstitial pregnancy. This type is probably exceeded in rarity only by the true ovarian pregnancy, and it makes up not more than 3 per cent of all ectopic pregnancies.

An interesting case of interstitial pregnancy, with an unusual feature, is herewith reported.

Mrs. L. M. (No. 75279), 30-year-old white female, was admitted to the hospital on Sept. 2, 1946, complaining of severe knifelike pain in the lower abdomen with radiation to the left shoulder. The onset was 9 A.M. of the admission date.

The present illness dated back to the June 9, at which time the patient had a dark brown thin vaginal discharge for one week. There was no pain or cramps associated with the discharge. Her last regular menstrual period had been on May 3. In July she had severe lower abdominal pain lasting several hours, which gradually subsided completely. Following this episode she consulted her obstetrician who suspected a pathologic pregnancy, since examination revealed the uterus to be irregularly enlarged in the left cornual region.

A consultant confirmed the findings already mentioned, and advised that the patient be carefully observed and conservatively treated at present. Accordingly, the patient was given progesterone and was watched.

On the morning of hospital admission the patient suffered severe knifelike pain in the lower abdomen referred mildly to the left shoulder. When admitted to the hospital two hours later she did not appear acutely ill. Temperature, pulse, and respirations were normal, and the blood pressure was 110/65.

The menstrual history revealed a normal thirty-day cycle. Her last regular menstrual period was May 3 lasting four days, and her previous period was on April 6 lasting four days. The patient had been married for seven years, her first pregnancy in September, 1942, terminated as a ruptured left tubal pregnancy. This tube was removed at operation. There were no subsequent pregnancies until the present one.

Examination of the abdomen revealed a mass, undoubtedly the uterus, which seemed to be drawn into the left lower quadrant, the height of the fundus being 15 cm. above the symphysis. The left cornual area was enlarged, tender, and firm. Rectal examination revealed a thick undilated cervix. Urinalysis was essentially negative and the red blood count was 3.03 million with 8.1 Gm. of hemoglobin. The Rh factor was negative.

In view of the rapidly improving general condition of the patient, and the strong desire of the patient to have a child, watchful waiting seemed advisable. The mass in the abdomen was checked frequently, and blood pressure, pulse, and respirations were recorded at frequent intervals.

The temperature ranged between normal and 99° F. The pulse between 64 and 80 and the blood pressure between 92/60 and 110/60. The patient was kept at bed rest with an ice cap to the abdomen, codeine and aspirin given in small doses, and progesterone in adequate dosage.

Under this regime the patient rapidly improved. A transfusion of one pint of compatible blood was given, and the pain rapidly subsided to a low-grade dull ache in the left lower quadrant. The patient was permitted to sit out of bed on the third hospital day. She was completely free of pain at this time, and the mass in the lower abdomen lost its tenderness and became much softer.

On the sixth day of her admission about 9:00 P.M., and following an effective bowel movement, the patient complained of severe lower abdominal pain. The abdomen was rigid and exquisitely tender. Blood pressure dropped to 60/34, the pulse was 80, but volume was poor. The skin was cold and moist. The patient was prepared for immediate operation.

Under general anesthesia the abdomen was opened. About 1,500 cubic centimeters of blood was aspirated from the abdomen. The sigmoid was found to be tightly adherent to the superior posterior portion of the uterus, which was bulging into a conical shaped mass predominately left sided. The sigmoid was partially separated from the uterus, and there was gross hemorrhage into the uterine wall with rupture of the uterus at this point. An incision was made enlarging the point of rupture and a well-formed fetus of about four months' gestation was removed. The sigmoid was then separated from the uterus, and a Porro section accomplished without further difficulty. During the operative procedure typed and matched blood was given continuously. The patient was in shock during the entire operative procedure, and left the operating room in poor condition. She was given a second infusion of compatible blood immediately after operation and her condition improved rapidly, blood pressure rising to 98/40. From this point on, the convalescence was uneventful, and the patient was discharged from the hospital on the thirteenth postoperative day.

The pathologic report showed a uterus amputated at the internal os having an odd lop-sided shape. The left border bulged into a conical shape, having for its apex the ovary. The fixed specimen measured 14 cm. by 10 cm. by 6 cm. The cavity in the fundus extended into the conical shaped bulge, but ended abruptly, being supported by a firm layer of uterine wall 1 cm. thick. Serial sections revealed a rough cavity partly collapsed within the uterine wall, but not contiguous with the uterine cavity. Part of this cavity was surrounded by uterine muscle. The top was supported by broad ligament, and the apical border was formed by the left ovary which in turn was incorporated by the walls of the uterus. The cavity was rough, being lined by fragments of placenta and clotted blood, and contained a well-formed placenta with cord. The stump of the right broad ligament was close to the uterus. The microscopic examination showed a decidual reaction of the endometrium and a decidual stroma in the wall containing well-formed chorionic villae.

*Diagnosis.*—Extrauterine pregnancy, probably in the cornu of the uterine wall (interstitial), expanding laterally with rupture into the fold of the broad ligament and peritoneal cavity.

## Department of Reviews and Abstracts

### Selected Abstracts

#### Cancer, Malignancies

**Cusmano, L.**: Nuclear Aspects in Crushed Cancer Tissue With Carmine Stain, *Atti della Societa italiana di ostetricia o ginocologia* 37: 167, 1946.

Structure and chemical make-up of chromosomes and nucleoli differ in cancer and in physiologic tissue. Selective absorption for ultraviolet light and selective staining properties of timonucleinic acid, the main component of the chromosomes, versus ribonucleinic acid, the main component of the nucleoli, made it possible to demonstrate this.

Investigations of cancer tissue made in ultraviolet light by Caspersson and Santesson resulted in the recognition of two main types of cells: "A" cells, as compared with healthy cells, show an increased content of timonucleinic acid and therefore have condensed and prominent chromosomes. "B" cells, that show diminution of timonucleinic acid and, therefore, have indistinct chromosomes.

Both are unbalanced types of cells. "A" cells are the superactive cancer cells in which condensed chromosomes with excessive timonucleinic content have the tendency to divide too frequently and too quickly. "B" cells are the exhausted regressive cancer cells with lack of timonucleinic acid in the chromosomes that have lost the capacity of reproduction.

Their recognition and their distribution in a tumor tissue is therefore most significant for diagnostic purposes as well as for the estimation of the degree of aggressiveness of a tumor.

Cusmano of the Gynecological Department of the medical school of Parma has applied to human cancer tissue a simple acetic-carmine stain, originated by Barigozzi for the study of chromosomes in *Drosophilae*, and the result was the demonstration of the morphologic characteristics of the metabolic variations seen by Santesso and Caspersson under ultraviolet light, with a simple method that can easily be applied in routine clinical investigations. According to Barigozzi's technique, the material is fixed in acetic acid-alcohol, crushed under cover-glass, and stained with acetic-carmine. The cytoplasm is dissolved and only the naked nuclei are apparent.

"A" cells show a perfectly regular nuclear membrane and numerous small intensely red stained granules, representing the chromosomal chromomeres with high timonucleinic content, and among them one or two larger, faintly stained vesicular bodies that represent the nucleoli.

"B" cells show an irregular nuclear membrane, few faintly stained chromomeres, with low timonucleinic content and two clumpy, deeply stained central bodies representing the hypertrophic nucleoli with an excess of stored ribonucleinic acid that has lost the capacity to be transformed so as to provide the chromosomes with the amount of timonucleinic acid necessary for reproduction.

Using the above carmine-acetic method, Cusmano studied the distribution of "A" and "B" cells and the aspect and frequency of typical and atypical mitosis in cancers of the

cervix and fundus, the nuclear structure of hydatidiform moles and of chorionepitheliomas and he also applied the method to the investigation of nuclear features in vaginal smears. The results of these observations are most significant and are reported in the following abstracts.

GEMMA BARZILAI.

**Cusmano, L.: Neoplastic Nuclear Features in Vaginal Smears Under Carminacetic Stain, Quaderni di Clinica Ostetrica e Ginecologia 2: 661, 1997.**

After a painstaking review of American contribution in the field of detection of genital malignancy by the use of vaginal smears, Cusmano reports a modification of his own carminacetic method for cytologic investigations as a new approach to identification of the exfoliated tumor cells in the vaginal secretion.

For the preparation of the smear, vaginal content is secured with a pipette as described in the original Papanicolaou procedure. The material is immediately diluted with a generous amount of 1:2 acetic acid-alcohol mixture, and then centrifuged. Then the fixative is disposed of. Acetic-carmine is added to the vaginal sedimentation material which is then crushed under a cover glass, dehydrated in alcohol, and mounted on a slide.

Smears prepared with the technique described above in cases of neoplasms of the female genitals and examined at a magnification twelve hundred times show:

1. Nuclei with a regular nuclear membrane, containing numerous small intensely red colored granules disposed at regular intervals and definitely recalling in their aspect chromomeres connected by the colorless linin in the uncoiled chromosomes, thus representing the proliferative "A" type of neoplastic cells described by Cusmano and Barigozzi in former papers.
2. Nuclei showing an irregular but intact membrane and containing one or two large, clumped, deeply stained nucleoli and indistinct chromomeres.
3. Intermediate forms linking the two above types one to another and showing a few rather distinct chromomeres usually dislocated toward the nuclear membrane and large clumped but faintly stained nucleoli.

Among these nuclei, which are always largely represented in the smears when a cancer of the uterus is present and which are interpreted by Cusmano as cancer cells at rest, a few typical and atypical mitotic figures in the varied phases of reproduction are usually seen.

Small connective-tissue cells and large histiocytes are always interspersed among the epithelial cells. The histiocytes appear faintly and uniformly stained and it is not hard to distinguish them from the regressive epithelial cells at rest which are morphologically somewhat alike.

Cusmano's cytologic approach to cancer diagnosis in vaginal smears is established on sound objective criteria. It may well prove a milestone in the pioneering work which still has to be done in the development of the method of isolated cells in secretions and body fluids, a method of investigation that, as Warren says, is "as old as cellular pathology but that has started being successful only with Papanicolaou's work in the past decade or so."

GEMMA BARZILAI.

### Gynecologic Operations

**Darner, C. B.: Surgical Sterilization in Women, The Journal-Lancet 68: 118, 1948.**

Pregnancy may follow Fallopian tube ligation if the suture material cuts through the tube and recanalization occurs. Nonabsorbable suture material permits this, and the author therefore recommends the use of catgut in the Pomeroy operation, No. 2 plain catgut being preferred because it induces more tissue reaction. In 141 cases sterilized by this method, there has been no failure. In cases of failure, the surgeon is not guilty of malpractice if "reasonable diligence" is exercised.

Without a medical indication, consent may be invalid because it undertakes to authorize an act contrary to public policy. Parity of four or more is considered an adequate medical

indication for sterilization, because the incidence of complications rises sharply after a fourth childbirth. This was the author's indication in one-half of the total series of 238 cases, the others being performed in the presence of various organic diseases. IRVING L. FRANK.

**Macaggi, G. B.: Lying on the Abdomen in the Aftercare of Surgical Interventions for Vesicovaginal Fistulas,** Archivio Italiano di Urologia 22: 114, 1947.

Keeping the bladder empty during the process of cure, or, in other words, avoiding infiltration of urine in the site of the reconstructed vesical wall, is the main problem of the post-operative care of vesicovaginal fistulas.

Urine infiltration never occurs after suprapubic incision of the bladder where the position of the lesion is such that urine does not come in contact with it. This lesion always heals spontaneously by granulation after the catheter is removed.

Keeping the patient lying on the abdomen while a retained catheter is in place avoids contact of the urine with the lesion, thereby creating a condition favorable for healing as in the case of suprapubic incision.

Macaggi used the "belly position" (which is accepted as a routine position in Italy) in two cases of fistulas that had been previously repeatedly operated upon without success.

Both cases healed: one by first intention and the other by granulations. The latter, quite an unusual event, should be borne in mind in cases of fistulas stubbornly resisting surgical treatment. According to the author, the "belly position" is to be credited for this success. GEMMA BARZILAI.

**Dellepiane, G.: A Vaginal Technique for the Combined Treatment of the Prolapsed and Retrodisplaced Uterus,** La Ginecologia-Scritti in onore del Prof. Ercole Cova.

Dellepiane, Director of the Lying-in Hospital and Medical School in Parma, describes a vaginal technique for the combined treatment of the prolapsed and retrodisplaced uterus in which a new step is added to a procedure that in the main corresponds to the operation generally known in this country as the Manchester operation.

A survey of operations heretofore described for the treatment of the prolapsed uterus is given, the contribution of the Italian school on this argument is stressed and credit is given to Pestalozza for focusing, as early as in 1902, attention on the significance of the shortening of the broad ligaments for the elevation of the uterus.

Dellepiane's operation consists of the following steps:

1. A "Y" incision is made in the anterior vaginal wall with the wide base slightly below the level of the inner os of the cervix and the other end about 1 cm. above the opening of the urethra. This is combined with a triangular incision in the upper and posterior vaginal wall with the apex at the cul-de-sac and the wide base at the same level as the anterior incision, thus marking the boundaries for a wedge-shaped amputation of the cervix.

The vaginal wall is separated from the pubic fascia. The bladder is separated from the pubic fascia and from the uterus until the vesicovaginal pouch is reached. Separation is then extended laterally and the broad ligaments are exposed. The cervical vessels are tied. Ureter slings are occasionally visualized. The bladder is pushed off. The uteropubic fascia is trimmed, or duplicated, and sutures are placed, catching the uterus only in the upper part. The cervix is not amputated at this step to avoid useless bleeding. This step takes care of the cystocele.

2. A triangular incision is now made in the posterior vaginal wall with the wide base at the perineum and its apex pointing to and almost touching the lower end of the above-described incision in the upper part of the posterior vaginal wall, a technical detail which permits an easy approach to sacrouterine ligaments.

The rectopubic fascia is severed and uterine insertion of the sacrouterine ligament is reached by gauze dissection on either side. Separation is extended laterally and downward and levator muscles covered by their fascia are visualized. Strong silk sutures are passed through the levator muscle and the upper two sutures also catch the sacrouterine insertion and the denuded isthmic portion of the uterus. The result of this step is an anatomically

correct fastening of the pivotal area of the uterus in the posterior part of the pelvis which draws the cervix backward and throws the fundus forward, thus correcting the retrodisplacement.

A wedge-shaped amputation of the cervix is now performed according to the previously assigned boundaries. The broad ligaments are duplicated and fastened at the isthmic stump. The cervix is rebuilt with vaginal wall tissue. The result of this step is elevation of the uterus and shortening of the cervix.

3. The rectovaginal fascia is now sutured. Vaginal walls are closed as in routine posterior colporrhaphy. This step, together with the levator suture, takes care of the rectocele, if existent, and of relaxation of the pelvic floor.

This operation has been carried on by Dellepiane for the past ten years. It has proved effective and does not interfere with pregnancy, or parturition. GEMMA BARZILAI.

#### Miscellaneous

**Kent, C. F.: Urine Versus Blood Serum in Friedman's Test for Pregnancy,** J. Missouri M. A. 45: 275, 1948.

There is considerable chance for error in the use of urine for making the Friedman test for pregnancy in ambulatory patients. Frequent causes of error are that: the patient may drink water after midnight, resulting in dilution of the hormone in the morning fasting specimen; there may be delay in taking the specimen to the laboratory, resulting in the dissipation of the hormone present and excessive bacterial growth; containers may be used that have previously contained other substances which cause the death of the test animal and necessitate a repetition of the test. When blood serum is used for the test, the blood is withdrawn at the laboratory and the serum used is freshly prepared in suitable containers; the blood specimen can be taken at any time of day, as the ingestion of fluid in ordinary amounts does not dilute the blood. In a study of 156 Friedman tests at one laboratory, it was found that in 81 urine tests, there were 33 positive (40.7 per cent) and in 75 blood serum tests, 41 positive (54.6 per cent). False positives are rarely a problem; it is false negatives that are of most importance. If errors in the collection of urine specimens could be entirely eliminated, the results of the two tests would probably be in agreement, but this is rarely possible in the average laboratory dealing with ambulatory patients. HARVEY B. MATTHEWS.

**Anderson, C. D., and Seldon, T. H.: Influence of Sex of Donors on Transfusion Reactions,** Proc. Staff Meet., Mayo Clin. 23: 149, 1948.

Hustin and Remy reported in the *Presse medicale* that in 80 reactions occurring in 864 transfusions, the incidence of reactions was higher when a woman was the donor; the highest incidence was observed when the blood of a woman donor was given to a woman recipient.

A review of the transfusions done at the Mayo Clinic in the first half of 1947 shows that in 2720 transfusions there were 139 reactions, an incidence of 5.1 per cent. With female donors the incidence of reactions was 5.7 per cent and with male donors, 4.6 per cent. While this difference in the incidence of reactions was small, considered in relation to the number of reactions, the rate was nearly 25 per cent higher with female than with male donors. With women recipients, the incidence of reactions was 5.8 per cent when a woman was the donor and 4.6 per cent when a man was the donor. With male recipients, the incidence of reactions was 5.6 per cent with a woman donor and 4.8 per cent with a man donor. These findings agree with those of Hustin and Remy, but do not indicate as great a difference between men and women donors as these authors report.

It is concluded that the sex factor is of no practical importance in blood transfusion, although the chances that a reaction will occur are somewhat higher when a woman is the donor. HARVEY B. MATTHEWS.

**Goldzieher, Joseph S.: A New Colorimetric Method for the Determination of Pregnadiol,** J. Lab. & Clin. Med. 33: 251, 1948.

A new method for the colorimetric determination of pregnadiol is described and its advantage over the Talbot sulfuric acid technique discussed. The accuracy of this new

method is said approximately to equal the sulfuric acid one and greater stability of color is claimed. The colorimetric reaction is based on the interaction of pregnadiol with acetyl chloride and zinc chloride in glacial acetic acid solution.

S. B. GUSBERG.

### Newborn

Wiener, Alexander S., and Gordon, Eve B.: **Studies on the Conglutination Test in Erythroblastosis Fetalis**, J. Lab. & Clin. Med. 33: 181, 1948.

The authors have studied comparatively a number of methods used for the detection of blocking ("univalent") antibodies; in the small group of cases presented, they have demonstrated the greatest sensitivity to result from the use of an albumin-plasma testing mixture, and they call this the albumin-plasma conglutination test. These studies suggest that the placental barrier readily permits the passage of this antibody, so that a good correlation between the maternal blocking antibody titer and the severity of the infant's erythroblastotic disease exists. This correlation does not appear to hold in the case of anti-Rh antibodies ("bivalent") whose passage through the placental barrier is more difficult, possibly depending on factors other than height of titer.

S. B. GUSBERG.

Mollison, P. L.: **Physiological Jaundice of the Newborn**, Lancet p. 513, April 3, 1948.

Studies on the survival of placental blood erythrocytes and of adult erythrocytes when introduced into the infant blood stream indicate that the breakdown rate of the infant's own red cells is twice that of adult red cells. This rate is independent of the degree of polycythemia present. The increased hemolysis probably depends on rapid destruction of immature types of erythrocytes present at birth, the bulk of the cells behaving like adult cells.

While bilirubin liberation is three times that in the adult blood stream, this rate could not produce the high bilirubin accumulation of clinical jaundice if the infant liver could excrete maturely. Bromsulfalein excretion in infants is retarded and jaundiced infants have reduced amounts of bile pigment in stool and urine. It is therefore reasoned that although increased hemolysis is present, the chief cause of physiologic jaundice of the newborn is a poor excretory capacity of the liver.

IRVING L. FRANK.

Wiener, A. S., and Brancate, G. J.: **Erythroblastosis Fetalis Caused by Double Sensitization to the Factors rh" and Hr'**, Anesthesiology 9: 175, 1948.

In some cases, an Rh-positive mother has given birth to an erythroblastotic infant; such cases are due to some unusual type of sensitization. Some of these cases have been traced to sensitization to the A and B factors, but others can be explained only on the basis of the so-called Rh-Hr blood types. As is now recognized, there are at least three Rh factors, Rh<sub>o</sub>, rh', and rh". The Rh<sub>o</sub> factor which is the original Rh factor is the most antigenic of these three factors. Blood of type rh does not contain Rh<sub>o</sub> factor, but it does contain at least two Hr factors, which are also present in most Rh-positive bloods.

In the case reported, the mother was Rh-positive and had five children living and well; the sixth child developed icterus gravis a few hours after birth; the child, as well as the mother, was found to be Rh positive. Complete blood grouping and Rh-Hr tests of the infant, when seven days old, and of the entire family showed all members of the family to be Rh-positive. The mother belonged to subtype Rh<sub>1</sub> Rh<sub>1</sub> and the infant to subtype Rh<sub>1</sub> Rh<sub>2</sub>, thus showing the factor rh" that was not present in the mother's blood. The mother also was Hr' negative, while the infant's blood contained Hr'. Tests on the maternal serum indicated that the mother was doubly sensitized to both rh" and Hr' factors. If it had been possible to determine that this type of sensitization was present prior to the birth of the infant, the child could have been treated by a complete exchange transfusion from a donor or group AB, and Rh<sub>1</sub> Rh<sub>1</sub> subtype. Cases of Hr sensitization are very rare, and the serum for testing is not generally available. Transfusions of Rh-negative blood had been given before these

blood studies were made; further transfusions from a type A B, Rh<sub>1</sub> donor supposedly Hr-negative were given, but this caused deepening of the jaundice, and it was found that no tests had been made for the Hr factor. The jaundice subsided and the infant survived, but examination at the age of six months showed definite evidence of permanent brain damage.

This case gives additional evidence of the importance of the constitution of the patient in iso-immunization. Only about one in fifteen Rh-negative individuals becomes sensitized to the Rh factor under the natural conditions in which only a minute amount of fetal blood enters the maternal circulation, so that only constitutionally predisposed women become sensitized. In the case reported, the mother was evidently constitutionally predisposed to iso-sensitization, as she showed sensitization not only to one, but to two factors present in the infant's blood and not in her own blood.

HARVEY B. MATTHEWS.

### Pregnancy, Complications

**Burnett, C. W. F.: Suprarenal Haemorrhage and Pregnancy**, Brit. M. J., p. 249, Feb. 14, 1948.

The author reports a case of massive suprarenal hemorrhage occurring in a 33-year-old gravida v, para i, who had had three abortions. She had been treated for a threatened abortion at two months and discharged in satisfactory condition. One month later, she was readmitted in vascular collapse, two hours after a spontaneous abortion. She died twenty minutes after admission. Autopsy showed bilateral massive hemorrhage of both adrenal glands.

The author briefly summarizes the three other reported cases in the literature, two of which occurred during pregnancy. The third occurred during the puerperium of a full-term pregnancy which had been complicated by mild pre-eclampsia.

The author challenges the opinion stated in the literature that massive suprarenal hemorrhage is associated with involutional changes in the adrenal glands. He feels the four cases now reported fail to provide sufficient evidence to substantiate this conclusion.

R. G. DOUGLAS.

**Ogden, J. Kenworthy: Retroperitoneal Haemorrhage in Pregnancy**, Brit. M. J., p. 389, Feb. 28, 1948.

The author reports in this article a case of massive retroperitoneal hemorrhage in pregnancy. A review of the six cases in the literature is given. The patient was a 25-year-old gravida ii, para i, who had delivered by breech delivery a 3,600 Gm. infant after a labor of thirty-six hours. The infant subsequently died of cerebral hemorrhage. The patient's antenatal course had been normal until approximately the thirty-six week, at which time she developed severe hypogastric pain followed by three convulsions and shock. The uterus became tense and tender. The case was considered to be antepartum eclampsia with premature separation of the placenta. The patient responded to antishock therapy, only to sustain a second episode of pain and shock twenty-four hours later. A classical cesarean section was performed and a macerated fetus delivered, there being a large retroplacental hematoma. Her immediate postoperative course was satisfactory. On the fourth postoperative day, she had a convulsion, went into a state of collapse, and died two hours later.

Postmortem examination revealed 2,250 c.c. of blood in the peritoneal cavity and a large retroperitoneal hematoma in the region of the pancreas and curvature of the duodenum. The exact site of the hemorrhage could not be determined.

The author's review of the literature reveals six previous cases, and five deaths. The deaths all occurred in cases in which the hemorrhage was in the region of the floor of the lesser peritoneal sac. The site of hemorrhage in the case surviving was in the pelvis. The fact that the author's case, as well as two previously reported, occurred in association with toxemia of pregnancy is pointed out. The author raises the question of the possibility of thrombotic processes in larger caliber vessels, such as is seen in the small vessels in eclampsia, and their being responsible for the hematoma in fifteen later cases.

R. G. DOUGLAS.

**Canna, S.: The Initial Nervous Syndrome in Wartime Pregnancies, La Ginecologia 13:**  
497, 1947.

Vomiting, marked irritability, insomnia, considered by Canna as the characteristic syndrome of severe cases of initial nervous impairments in pregnancy, showed a marked decrease during wartime and the number of pregnant women showing no nervous disturbances during the first months increased remarkably.

The rate of severe nervous syndrome cases decreased from 20 per cent prewar to 6 per cent during the war; and conversely, cases of expectant mothers who showed no nervous impairment increased to 35 per cent, as compared with 25 per cent before the war.

This decrease of nervous symptoms during the war was not influenced by social or economic factors. It affected equally factory worker, farmer, and housewife.

Canna credits this remarkable reduction in nervous symptoms in the initial stage of pregnancy during the war to the reduction in fat and animal protein in nutrition. The psychological factor might have played an important role.

GEMMA BARZILAI.

### Radiation

**Wells, J. J., and Popp, W. C.: The Use of Pyridoxine Hydrochloride in the Treatment of Radiation Sickness, Proc. Staff Meet., Mayo Clin. 22: 482, 1947.**

The use of pyridoxine hydrochloride (vitamin B<sub>6</sub>), given intravenously in the treatment of radiation sickness in 200 patients undergoing intensive roentgen-ray therapy, is reported. Twenty-seven of these patients were under treatment for carcinoma of the breast; fifteen for carcinoma of the cervix; six for carcinoma of the uterus; and nine for carcinoma of the ovary. This medication was given to patients who had nausea and vomiting during the course of radiation therapy, or to a few patients who had had radiation sickness during a previous course of treatment. The best results were obtained with a dose of 100 to 200 mg. given about half an hour before each roentgen treatment; the larger dose was used when treatment was given to the abdomen, thorax, or pelvis. In twelve cases of radiation sickness, placebo injections of sterile water were given; these placebos did not relieve symptoms in any case when substituted for the pyridoxine hydrochloride injections. In eighteen of the cases treated, results of the treatment were excellent; i.e., all symptoms of radiation sickness relieved; in 111 cases, results were good, nausea and vomiting relieved but some malaise persisting; in 52 cases, results were fair, nausea occurring occasionally; there was no relief of symptoms in 19 cases, 9.5 per cent. When radiation sickness was controlled, most patients were able to tolerate a heavier daily dosage of radiation, so that the duration of the treatment could be shortened. No toxic reactions or complications due to the administration of pyridoxine hydrochloride were noted in any case. The high percentage of favorable results in this series justified the continuance of pyridoxine hydrochloride in the treatment of radiation sickness.

HARVEY B. MATTHEWS.

### Erratum

In the article, "Normal and Cystic Structures of the Broad Ligament," by Drs. Gardner, Greene, and Peckham, issue of June, 1948, page 930, paragraph 2, third sentence, "it had undergone a *modern* amount of cystic dilatation," should read, "it had undergone a *moderate* amount of dilatation."

## Correspondence

### Structure of the Broad Ligament

*To the Editor:*

I have read with a great deal of interest Dr. Gardner's recent contribution on the structures of the broad ligament which appeared in the June issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

All will agree that eponymous nomenclature has many drawbacks, especially when applied to diseases and operations. In describing anatomic structures, however, proper names are often no more than localizations in the "geography" of the body and hardly more objectionable than proper names for cities or geographical areas. We could designate every spot on earth by its latitude and longitude but what a cold world that would make. Besides proper names in medicine *do* teach medical history.

I sympathize fully with Dr. Gardner's objection to the multiplicity of proper names but his attempt to reform nomenclature is a lost cause. We shall never be able to do without proper names unless we use tremendous circumlocutions. Witness, for example, the nomenclature of such fields as paleontology, ornithology, and botany.

There is, however, to my mind, a greater objection to Dr. Gardner's nomenclature in the present instance. He uses embryologic terminology for adult structures. The embryologist must use the terms mesonephric (really pronephric when it concerns the duct) and para-mesonephric because when these systems develop the sex of the zygote is not yet determinable and the dominance of one or the other of the two duct systems in doubt. Certainly the Müllerian duct must be the "para" system, since it not only develops later but in some lower forms develops from the mesonephric tube. However, after the female sex of the fetus has been established, the oviduct is no more a paramesonephric duct than a living elephant is a paramastodon.

Another point, it is extremely hazardous to predicate histogenesis on histologic appearance. Even physiologic reaction is no safe criterion. (Moench: Surg., Gynec. & Obst. 49: 332, 1929.) Adenomyosis of celomic origin shows the same hormonal response as the endometrium itself—and what of vicarious menstruation? Villi may develop on the peritoneal surface of the oviduct and it is immaterial whether they grow out from the tube or develop from the peritoneum (Moench, loc. cit.).

The "Müllerian" duct system is essentially a simple tubular affair but the mesonephric system is very complicated. Anyone who is familiar with the extreme rarity of true reduplications of the "Müllerian" ducts in the adult must be most reluctant to accept the numerous accessory oviducts which Dr. Gardner describes, even though it is certain that aberrant "Müllerian" tissue does occur in the broad ligament (Moench, loc. cit.).

Dr. Taylor has stressed the growth potentialities of the celomic epithelium. We find decidual reactions here and cell rests that simulate stratified squamous epithelium. May not, then, some of the accessory oviducts of Dr. Gardner be but celomic invaginations? While tubal diverticuli, when they reach the surface, acquire fimbriae, may not celomic invaginations do the same? Certain areas of the body seem destined to form a certain type of epithelium. I have seen a row of typical "Wolffian" duct cysts in the vagina, some of which were lined by squamous epithelium. Other cysts of the same origin contained blood. I have removed an epoophoron cyst which showed columnar epithelium and a few wartlike papillae (not villi) similar to those seen in serous cystadenomas of the ovary. It is difficult to assume that in this location of the broad ligament there should be accessory ovarian tissue. Tubules such as Dr. Gardner describes in the hilum of the ovary I cannot but regard as of mesonephric

origin regardless of the epithelial lining. It is difficult to assume anything else. A "Müllerian" duct branch in this location would have to be a tremendous structure comparatively unless we assume a phylogenetic atavism to such a form as salamander ater.

The pronephric duct becomes the mesonephric duct. The pronephros is an evanescent, small group of cells high in the abdomen. The mesonephros is much larger and extends lower. I personally believe that the "hydatid of Morgagni" is the unused, unabsorbed upper portion of the pronephric duct. That will explain its great frequency of occurrence. Were this structure paramesonephric, why has no one ever seen fimbriae surrounding its end? To say its end is closed is no explanation, it was open originally. The more mesially placed small cysts of the broad ligament seemed to stem, at least in the cases I have examined, from the epoophoron tubules.

In conclusion, I want to thank Dr. Gardner for a most interesting presentation, even if at present I cannot see eye to eye with him. Might I add that it is Keibel and Mall's *Embryology*, not Kiebel and Malls'.

G. L. MOENCH, M.D.

27 WEST 55 STREET,  
NEW YORK, N. Y.  
July 8, 1948.

#### Reply by Dr. Gardner

To the Editor:

We are pleased that Dr. Moench is in sympathy with our objection to the multiplicity of proper names for broad ligament structures and cysts; furthermore, we doubt that their usage is of notable importance even in the teaching of medical history.

He objects to the use of embryologic terms for structures found in the adult, yet the rete of the embryonic ovary is still called the rete in the adult ovary. Therefore, we fail to recognize consistency in his objection to the use of similar embryologic terms for persisting but nonfunctional structures in the adult ligament.

His proposal to use "paramesonephric" duct prior to the time of sexual differentiation and another term after the sex of the embryo can be recognized (even though the embryo is now only a few weeks older) would not add clarity to this subject. We doubt, though, that he really intended to use "oviduct" for this latter term (Paragraph 4, last sentence) since "ovduct" is an accepted term for a derivative of only a part of this duct; i.e., the uterine tube or oviduct.

We also are "familiar with the extreme rarity of true reduplication of the 'Müllerian' ducts in the adult." We presume Dr. Moench means true reduplication of the oviducts rather than "Müllerian" ducts, since this latter term should mean true reduplication of all derivations of the duct. However, we fail to see what the rarity of true reduplication of the oviducts has to do with the frequency of accessory oviducts. The formation of true reduplication of the oviducts represents a difficult and complex embryonic feat. The mechanism of formation of accessory oviducts is entirely dissimilar.

In addition, "the numerous accessory oviducts which Dr. Gardner describes" were specifically stated as being found in eleven of the 598 routine specimens, and in two of the eleven serially sectioned specimens. Perhaps our concept of the word "numerous" differs from that of Dr. Moench. Actually, however, the incidence is probably much higher than our data indicate, since routine sections would not necessarily include accessory oviducts. Perhaps we should emphasize that accessory oviducts are small, are not conspicuous, are recognized only when sought, are miniatures of the normal oviduct, and do not even approach in size and conspicuousness the "true reduplications" of the oviduct.

The remaining paragraph requires several comments:

"May then not some of the accessory oviducts of Dr. Gardner be but celomic invaginations?" If Dr. Moench means celomic invaginations in the embryo in or adjacent to the region of the primary ostium of the future oviduct, we agree. It is exactly the point we were trying to make in explaining the histogenesis of accessory oviducts. If he is referring

to "celomic" invaginations in the postembryonic or adult, we cannot agree. We grant the growth potentialities of this epithelium, and its probable importance in the formation of endometriosis, or endosalpingosis. Its ability to form a miniature replica of the oviduct with fimbria and well-differentiated inner and outer muscle layers seems unlikely.

We cannot follow Dr. Moench's logic in claiming that frequent occurrence of the hydatid of Morgagni is explained because it is derived from the "unused, unabsorbed upper portion of the pronephric duct." This belief would first necessitate evidence that this portion of the pronephric duct frequently persists. On the other hand, there is no doubt that a cranial remnant of the mesonephric duct (which we would prefer to call it rather than pronephric duct) may *rarely* persist. In one of our younger embryos we have observed such an isolated, semi-pedunculated cranial remnant. Dr. Moench may not have noted, but in our original report we stated that in an adult specimen, one of the pedunculated cysts in the region of the oviduct had simple cuboidal epithelium with a basement membrane and that we believed it to be a mesonephric duct remnant. This epithelium, by the way, is identical to that of the mesonephric duct found normally in the adult broad ligament. It is extremely difficult to believe that this hydatid, and the others which had epithelium identical to that of the endosalpinx, had a common single histogenesis.

G. H. GARDNER,  
R. R. GREENE, and  
B. M. PECKHAM.

CHICAGO  
Oct. 13, 1948.

## Necrology

Charles Russel Robbins, M.D., of Richmond, Va., Emeritus Professor of Gynecology at the Medical College of Virginia, died Oct. 16, 1948, at the age of 80 years. A graduate of the Medical College of Virginia in 1894, a founder and head of the Stuart Circle Hospital, member of various professional societies, surgeon of the Richmond Light Infantry in World War I, Dr. Robbins retired from active practice in 1946.

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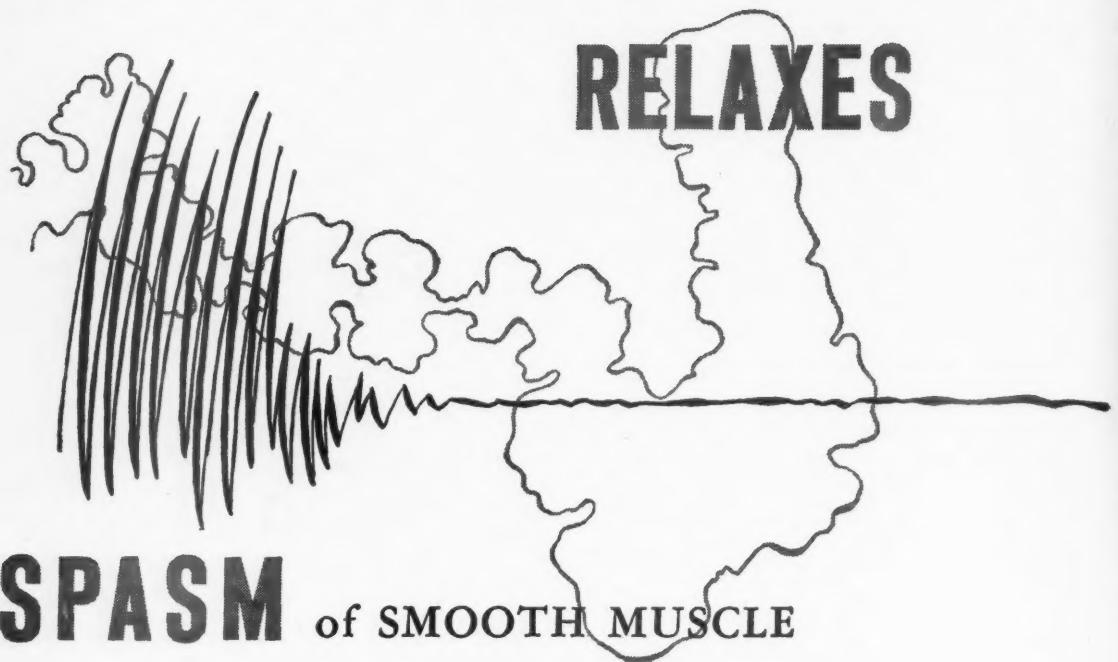
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